Eric E. Simon *Editor*

Hyponatremia

Evaluation and Treatment

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To my wife Cathy Lazarus and children,
Stuart and Karen.

Preface

Hyponatremia is a common medical condition that crosses all disciplines. This volume is intended to appeal to a wide cross section of the medical community. The emphasis is on the management of hyponatremia from diagnosis to treatment. Basic studies are included insofar as they enhance understanding of the clinical management. I have been fortunate to enlist the help of many of the world's experts on the topic.

By design, each chapter was written so it may be read in isolation. As such, there is some inevitable overlap. The first chapter summarizes the magnitude of the problem of hyponatremia in various clinical settings with some attention paid to etiologies and outcomes. Chapter 2 provides a comprehensive approach to the patient with hyponatremia. The concept of electrolyte-free water, relevant to both the pathophysiology and treatment, is next presented to expound on this concept in more depth than provided in other chapters. The controversial issue of renal/cerebral salt wasting is presented in Chap. 4. After these introductory chapters, the major consequences of hyponatremia, namely central nervous system manifestations, are discussed. This includes the direct effects of hyponatremia, the adaptations to hyponatremia, and the potential adverse effects of treatment, namely osmotic demyelination. Next follow chapters on hyponatremia in various settings including medications, heart failure, cirrhosis, psychosis, and exercise. The latter topic has now entered the lay public's awareness. Finally, there are two chapters on treatment. Chapter 11 specifically discusses the use of the new ADH analogs, the vaptans. At this time, the indications for use of vaptans are still fluid. The final chapter provides a comprehensive approach to treatment which provides a guide through this hazardous minefield.

New Orleans, LA, USA — Eric E. Simon, MD

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Chapter 1
Epidemiology and Significance of Hyponatremia

Federico J. Teran and Eric E. Simon

Introduction

Hyponatremia is a common electrolyte disturbance encountered within different clinical scenarios and populations. Its incidence and prevalence is influenced by the degree of hyponatremia and the available sodium measurements. We will assess the presence of hyponatremia along with its etiology and its impact on morbidity and mortality within the select literature.

Population Studies in Various Clinical Settings

Hospital and Community Settings

Hyponatremia is commonly encountered in the hospitalized patient and, to a lesser degree, within the community. In one of the largest comprehensive studies, Hawkins evaluated 120,137 Singapore patients for the prevalence of hyponatremia in both the hospital and community [1]. Within the community, he noted hyponatremia in about 4–7 % of the patients presenting to a primary care clinic. A similar number of hyponatremic patients [2] are seen in the emergency department (ED), but one-third of these patients (1.4 % of total) have a plasma sodium <125 mEq/L which is ten times higher than what Hawkins reported in the community. This higher frequency

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Table 1.1 Hyponatremia within the general population in community and hospital settings determined by sodium levels used to define hyponatremia

Population studies				
Reference	Sodium	Frequency (%)	Sample size	Study type
Community				
Hawkins [1]	<136	7.2	24,027	R
Hawkins [1]	<135	4.3	24,027	R
Hawkins [1]	<126	0.14	24,027	R
Emergency department				
Lee [2]	<134	3.8	3,784	P
Lee [2]	<125	1.4	3,784	P
Hospital				
Hawkins [1]	<136	42.6	43,249	R
Hoorn [3]	<136	30	2,907	P
Anderson [4]	<130	2.5	Unknown	P
Hawkins [1]	<126	6	43,249	R
Hoorn [3]	≤125	3	2,907	P
Intensive care unit				
Hoorn [3]	<136	38	2,907	P
DeVita [5]	≤134	29.6	98	P
Funk [6]	<125	1.2	151,486	R
Hoorn [3]	≤125	2	2,907	P

R retrospective study, *P* prospective study

of moderate hyponatremia correlates with a sicker population as two-thirds of the patients in the ED have hypovolemic hyponatremia due to gastrointestinal losses.

In the hospital setting, hyponatremia is more prevalent and severe. A number of studies (see Table 1.1) show that about 30–40 % of all hospitalized patients have some degree of mild hyponatremia [1, 3]. These studies suggest that mild hyponatremia is common in hospitalized patients, but there is a question of the actual incidence, as sodium measurements are missing in as many as half of the patients that may be at risk for developing hyponatremia [4].

Even with this discrepancy in sodium measurements, moderate hyponatremia is encountered in 2–6 % of patients depending on the cutoff level [1, 3, 4, 7]. About half of these patients have hyponatremia on admission while the other half developed it during their hospitalization [1]. When it comes to severe hyponatremia, Hawkins [1] noted that 1.2 % of all patients had serum sodium <116 mmol/L while Anderson et al. and others have reported a plasma sodium <120 mEq/L in about 0.5 % of the patients on admission [4, 7, 8]. Although this prevalence is low, again, it is about ten times higher than what is seen in the community [1].

The frequency of hyponatremia in the intensive care unit (ICU) is similar to the general hospital population (see Table 1.1) with 30–40 % having some degree of mild hyponatremia [5, 6, 9]. Severe hyponatremia in the ICU is similar to what is seen in the general hospital setting [3].

The etiology of hyponatremia varies depending on the clinical setting. Those presenting to an ED had mostly hypovolemic hyponatremia. As one transitions to admitted patients, the etiology changes to include a larger number of patients with drug-induced hyponatremia [3]. In the ICU setting and with severe hyponatremia, the causes now include a high level of antidiuretic hormone (ADH) secretion, which may or may not be appropriate, along with more hypotonic fluid administration and subsequent hospital acquired hyponatremia [3]. The number of patients that develop symptoms as a result of iatrogenic hyponatremia has been reported as high as 36 % with 19 % of these patients dying [3].

Hyponatremia is associated with adverse outcomes, and a delay in treatment can result in increased adverse events. Hoorn et al. [3] specifically examined hospital-acquired hyponatremia and found patients had a longer time to initiation of treatment and, consequently, a longer hospital stay. Hyponatremia is also considered to be a marker for underlying illness, and the severity of the hyponatremia may parallel the magnitude of the underlying disease which impacts mortality. A prospective study [10] of acutely hospitalized elderly patients with mild hyponatremia found no difference in 3-month mortality, compared to normonatremic patients, once adjusted for comorbidities. However, for moderate hyponatremia, in-hospital mortality was twice as high (16 %) compared to those without admission hyponatremia [7]. Similarly, Gill et al. [11] showed a threefold higher (27 %) mortality associated with severe hyponatremia (serum sodium <125 mmol/L). Acquired hyponatremia in the ICU also doubles the risk of mortality [9]; ICU-acquired hyponatremia has been associated with an 18 % ICU mortality compared to 9 % in those who always had normal sodium, and these patients also had higher hospital mortality (28 % vs. 16 %). Waikar et al. [8] evaluated patients to see if an improvement of hyponatremia translated to improved outcomes and noted that mortality (in hospital, 1-year and 5-year) was slightly better for those that corrected their hyponatremia during the hospitalization compared to those with persistent hyponatremia, though it was best for those who were always normonatremic.

Hyponatremia increases mortality risk but the exact relationship is unclear. Mortality may be attributed to the underlying disease, and the severity of hyponatremia may indicate progression of disease and result in worse outcomes. Hyponatremia can cause harm and present with symptoms such as confusion, nausea, vomiting, or seizures and can result in direct central nervous system (CNS) injury and death if not recognized and treated in time.

Postoperative

Healthy individuals can develop hyponatremia postoperatively with detrimental outcomes as reported by Arieff [12] in his study of 15 previously healthy women whom he encountered during a 10-year time span. The women underwent elective surgery with average preoperative serum sodium of 138 mmol/L and subsequently developed seizures and respiratory arrest postoperatively with average serum

Table 1.2 Hyponatremia within the postoperative patients

Postoperative				
Reference	Sodium	Frequency (%)	Sample size	Study type
Caramelo [14]	<135	12.5	112	P
Chung [15]	<130	4.4	1,088	P
Herrod [16]	<130	2.9	1,383	P
Madiba [17]	<130	2.2	71	P
Widjicks [13]	<130	0.004	290,815	R

R retrospective study, *P* prospective study

sodium of 108 mmol/L. The postoperative fluid balance was positive 7.5 L, and the urine sodium and osmolality suggested the syndrome of inappropriate antidiuretic hormone (SIADH). Hyponatremia was suspected as the cause of symptoms in one-third of the women, prompting early treatment. The other two-thirds had a delay of treatment of about 16 h mainly due to lack of recognition of symptomatic hyponatremia. Four of these women died and nine remained in permanent vegetative state. The other two patients recovered with significant neurological deficits.

Following Arieff's report, a large retrospective study at the Mayo clinic [13] examined the incidence of postoperative hyponatremia in 290,815 procedures on women over a 16-year period. They identified 1,791 women with cardiopulmonary resuscitation, new-onset seizures, central pontine myelinolysis, or metabolic encephalopathy. Only 11 patients within this subgroup had hyponatremia indicating an overall percentage of only 0.004 %. Interestingly, none of the 1,498 women with cardiac or respiratory arrest had hyponatremia.

Since then, there have been a number of prospective studies (see Table 1.2) looking at hyponatremia in the postoperative setting. One study [15] found 4.4 % of patients with a plasma sodium <130 mEq/L. Most of these patients were normovolemic, and 94 % were being given hypotonic fluids when they developed hyponatremia. Similarly, in a study by Madiba et al. [17] 2.2 % of 71 patients had a serum sodium <130 mmol/L, although one-fourth had documented hyperglycemia. None of the patients had a serum sodium less than 110 mmol/L and none developed neurological symptoms. Most episodes of hyponatremia occurred in normovolemic patients receiving hypotonic fluids.

Hyponatremia is associated with the use of hypotonic fluids in patients undergoing transurethral resection of the prostate (TURP) for the treatment of symptomatic benign prostatic hyperplasia (BPH). Traditional treatment has used a monopolar TURP which requires a nonconductive, electrolyte-free irrigation fluid (glycine, sorbitol, or mannitol). Occurrences of symptomatic hyponatremia (serum sodium <125 mmol/L) have been reported in about 2–7 % of patients undergoing this procedure. However, the use of bipolar transurethral resection, which uses isotonic saline, has minimized this rate to almost zero [18]. Similar accounts have been documented in female patients undergoing operative hysteroscopy, which require large amounts of a distention medium during surgery [19].

Table 1.3 Hyponatremia in the elderly in various clinical settings determined by sodium levels used to define hyponatremia

Elderly Patients				
Reference	Sodium	Frequency (%)	Sample size	Study type
Population Study, 55+				
Sajadieh [21]	≤137	9.2	671	P
Hoorn [22]	<136	7.7	5,208	P
Sajadieh [21]	≤134	2.1	671	P
Nursing home, 60+				
Miller [23]	≤135	18	119	R
Hawkins [1]	<135	18.2	51,659	R
Hospital, 65+				
Frenkel [10]	<135	34.3	895	P
Anpalahan [24]	<135	25	172	P
Byatt [25]	<130	6.9	929	P
Terzian [7]	<130	3.5	4,123	R
Shapiro [26]	≤125	6.2	86	P
Terzian [7]	<120	0.8	4,123	R
Hawkins [1]	<116	0.44	51,659	R

R retrospective study, *P* prospective study

Although hypotonic fluids have been implicated as a possible cause of hyponatremia in postoperative patients, several studies have rigorously examined this hypothesis and found that patients who developed hyponatremia are not necessarily given more hypotonic fluids than their normonatremic counterparts but, rather, these patients retain more water [14, 16, 20]. The results of these studies are consistent with transient SIADH due to pain and/or drugs which explains why patients given isotonic fluids also retain water [20].

In summary, the incidence of postoperative hyponatremia seems to be small and a large portion of the hyponatremia develops as a consequence of SIADH and administration of hypotonic fluid, although isotonic fluid may also cause hyponatremia in the setting of elevated ADH.

Elderly

Various articles reported on the incidence of hyponatremia in the elderly but used inconsistent definitions and within differing age distributions (see Table 1.3). As a consequence, there are mixed results in terms of incidence, prevalence, and its impact on morbidity and mortality. The etiology and contributing factors are also important for better management and treatment. The chronicity and acuity have not been elucidated in these studies and may play a role in terms of symptoms and outcome.

Two large population-based studies evaluated patients aged 55 and older and showed a frequency of mild hyponatremia of less than 10 % [21, 22]. There was a higher frequency of diuretic use in the hyponatremic groups compared to the controls [21, 22]. Miller et al. [23] looked at hyponatremia in a nursing home population, 60 and older, via a retrospective record review and prospective study. They found 18 % of patients had a serum sodium $\leq$135 mEq/L, the same as what Hawkins' [1] found in his older than 60 group, compared to an age-control ambulatory group of 8 %. When they examined all the sodium measurements for the past 12 months, 53 % of the patients had at least one episode of hyponatremia, and it was more common in a variety of CNS disorders and in 100 % of those with spinal cord injury. Surprisingly, no difference was noted between the hyponatremic and normonatremic groups in terms of cardiovascular disease, diabetes, or diuretic use. They also prospectively evaluated 23 hyponatremic patients with a water loading test and found abnormal water handling in 18 patients with an impaired urinary diluting ability compared to healthy controls consistent with SIADH.

Other studies have looked at patients age 65 and older in the hospital setting with varying severity of hyponatremia. Prospective studies found one-fourth [24] to one-third [10] of patients have mild hyponatremia (serum sodium <135 mmol/L) with SIADH as the etiology in half of the cases [24].

Moderate hyponatremia (serum sodium <130 mmol/L) is also present in a significant number of elderly patients. A study of 1,000 consecutive geriatric (65 years old and older) admissions [25] found hyponatremia in 7 % of all patients. Notably, half of the hyponatremic patients were receiving diuretics. A large retrospective study [7] noted a serum sodium <130 mmol/L in 3.5 % of the patients with women having almost twice the incidence (4.6 % vs. 2.6 %). A prospective, observational study [26] found 6 % of hospitalized elderly patients with a serum sodium $\leq$125 mEq/L. They found no increase of hyponatremia with age, but there were again twice as many females as males (8 % vs. 4 %) though women were nearly twice as likely to use thiazides and antidepressants compared to men. The most common contributing cause of hyponatremia was SIADH in about 60 % of the patients but multifactorial in half of the patients. Severe hyponatremia is uncommon in this population, seen in <1% of all patients [7] older than age 60.

Hyponatremia can contribute to falls and fractures in the elderly. Gankam Kengne et al. [27] performed a case control study of 513 cases with bone fractures after incidental falls in ambulatory patients 65 and older. They noted a serum sodium <135 mEq/L in 13 % vs. 3.9 % of controls. These were admissions for bone fractures. Hyponatremia was mild and asymptomatic and generally due to drugs (36 % diuretics, 17 % SSRI's) or SIADH (37 %). Hyponatremia was associated with falls in the ambulatory elderly with an odds ratio of 4.2 (adjusted). In the Rotterdam Study [22], hyponatremic elderly patients had more falls (24 % vs. 16 % for normonatremic patients) at baseline, and they had an increased risk of vertebral fractures and incident non-vertebral fractures even though there was no association with a lower bone mineral density in this group.

The cause of hyponatremia in the elderly population is often multifactorial. SIADH is the single leading cause of hyponatremia in 37 % to 78 % of the cases

[23, 24, 26, 27]. This is confounded by the use of diuretics in this population which ranges from 15 % to 43 % [21, 22, 25, 27]. Older age can also be a factor in the development of hyponatremia which may be due to a reduced capacity of the kidneys to handle free water [23]. Women have a higher incidence of hyponatremia in this group, but this is also associated with a higher use of drugs that impact the kidney's diluting ability or may cause SIADH.

Morbidity and mortality is significant in this population, and hyponatremia may be a contributing factor but the reports are mixed. There are studies that show an increase in adverse effects as hyponatremia worsens [21] along with a twofold increase in mortality [7, 22] and increase in falls [27], but other reports show no association between hyponatremia and increased mortality [10, 23, 25] even when severe [26].

Pediatrics

Hyponatremia within the pediatric population can result in subsequent neurological complications due to brain edema. It is seen in CNS and lung pathology and in gastrointestinal losses, and is also iatrogenic due to fluid administration in the hospitalized child. Some report hyponatremia (serum sodium <135 mEq/L) in one-fourth of hospitalized children [28]. Hoorn et al. [29] evaluated data from all children who presented to the ED in a 3-month period and noted a plasma sodium <136 mmol/L in 8.2 % of the 1,586 patients with at least one sodium measurement. About 70 % had hyponatremia on admission, and the rest developed it during their hospital stay. During a case-controlled portion of the study, they noted that children with hospital-acquired hyponatremia received almost as twice as much electrolyte-free water and total volume than their controls. Symptoms were mild; mainly headache and vomiting, but two children had significant neurological sequela. One child with a seizure disorder developed seizures during the hyponatremic episode, and another child had a cardiac arrest and died. Post-mortem analysis revealed brain edema.

These studies show that hyponatremia is common in the pediatric population and more pronounced when more electrolyte-free water is given.

Gender

Arieff's [12] study, discussed above, detailed the detrimental outcomes of 15 previously healthy women with hyponatremia in the postoperative setting. This led various authors to examine the role of female sex in the development of hyponatremia. Some studies show a relationship between female sex and the development of hyponatremia [2, 12, 20, 26] while others do not support this association [13, 30, 31]. One prospective study found a twofold higher frequency

of hyponatremia in women than in men, but the women were using twice as many diuretics and selective serotonin uptake inhibitors (SSRI's) than males. Nevertheless, it is still unclear why women develop hyponatremia more frequently than men, but it may be that there are confounding factors such as hormones, medications that cause hyponatremia, and a low body mass index (BMI). In marathon runners, female sex may be a possible risk factor, but this is also confounded by a lower BMI and a longer race time that may lead to more fluid consumption [30].

Specific Conditions

Central Nervous System Disorders

Hyponatremia is known to occur with various CNS abnormalities, and the etiology can differ depending on the underlying disease.

Sherlock et al. [32] reported on hyponatremia in various neurosurgical patients and found an incidence of 11 % for a plasma sodium <130 mmol/L in this retrospective study of 1,698 patients. Hyponatremia was present in 6.3 % of patients with pituitary disorders, 20 % with subarachnoid hemorrhage, and 9.6 % in those with traumatic brain injury. The etiology was due to SIADH (62 %; though 16.6 % were drug associated), hypovolemia (27 %), cerebral salt-wasting syndrome (CSWS) (4.8 %), fluid administration (3.7 %), and mixed SIADH/CSWS (2.7 %). Those who were hyponatremic had a longer hospital stay compared to normonatremic patients (19 days vs. 12 days, respectively). Severe hyponatremia was infrequent in this group; only 0.6 % of all the patients had a plasma sodium <120 mmol/L.

Pituitary surgery can be complicated by diabetes insipidus (DI) leading to polyuria, hyponatremia, or a combination of these two. Hensen et al. [33] reported on a series of 1,571 patients after transsphenoidal surgery for pituitary adenomas. Hyponatremia (serum sodium ≤132 mmol/L) was present in only 2.7 % of the patients on postoperative day 1 with subsequently more patients on day 7 (5 % of total); however, 40 % of the hyponatremic patients in the latter group were given desmopressin after surgery for treatment of polyuria. Overall, 8.4 % of the patients developed hyponatremia at some point up to the 10th postoperative day. Of these, a quarter developed symptomatic hyponatremia, but it was generally mild (nausea, headache, lightheadedness, vomiting) and transient. The etiology of hyponatremia was not elucidated, but the authors speculated that hyponatremia immediately after surgery was due to an acute release of arginine vasopressin (AVP) from pain or other non-osmotic stimuli whereas the delayed hyponatremia resulted from AVP release from an injured posterior pituitary gland (though some of the latter cases may have been drug induced). Kristof et al. [34] prospectively studied 57 successive patients undergoing transsphenoidal adenomectomy. Nine patients (16 %) had diabetes insipidus followed by hyponatremia (serum sodium <135 mmol/L), and

two of these patients had a second episode of DI. Isolated hyponatremia was present in 12 (21 %) of the patients with half developing mild clinical symptoms including headache, fatigue, nausea, and, in some, revulsion to drinking fluids. The patients had nadir median serum sodium of 132 mmol/L on day 9. SIADH was thought to be the cause of the hyponatremia as the ADH levels were not suppressed in these patients. One of the distinguishing parameters between SIADH and CSWS is that fluid restriction can result in volume depletion in those with CSWS due to continued natriuresis. In this study, one patient developed renal failure during fluid restriction possibly due to CSWS, though this possibility was not explored. SIADH seems to play a role in the pathogenesis of hyponatremia in this population, but the incidence of CSWS remains uncertain.

Hyponatremia with subarachnoid hemorrhage (SAH) due to a ruptured aneurysm is well documented. These patients are susceptible to cerebral vasospasm with subsequent cerebral infarction. Hyponatremia is important in these patients as it may be due to CSWS which can lead to volume depletion and potentiate vasospasm and cerebral infarction. Sayama et al. [35] performed a retrospective study in 169 patients evaluating the site of the hemorrhage and the incidence of hyponatremia. Overall, one-third of the patients developed hyponatremia (serum sodium $<$135 mEq/L). Interestingly, half of the patients with a rupture in the anterior communicating artery developed hyponatremia compared to about 20 % in the other sites. The authors suggested this disparity may be due to the fact that the posterior hypothalamus is perfused by branches from the anterior communicating artery, and vasospasm of these arteries can lead to hypothalamic dysfunction. Hasan et al. [36] evaluated 208 consecutive patients and found that 34 % of the patients developed hyponatremia (serum sodium $<$135 mmol/L) after SAH with a higher frequency of cerebral infarction noted in the hyponatremic group compared to the normonatremic group (24 % vs. 12 %, respectively).

Hyponatremia is also associated with traumatic brain injury (TBI) and can lead to neurological dysfunction and possible long-term sequela. In prospective studies, hyponatremia (plasma sodium $<$130 mEq/L) occurs in 20–30 % of patients [37, 38]. Half of the hyponatremic patients had at least one measurement below 125 mEq/L, and the average time to first detection of hyponatremia was 6 days [37]. Hyponatremia may occur in a variety of types of head injury including cerebral contusion, acute and chronic subdural hematomas, acute epidural hematoma, and diffuse axonal injury [39], but others [38] found that intraparenchymal lesions were the most common type (89 %).

The etiologies for hyponatremia differ among TBI patients with reports of SIADH, CSWS, and hypopituitarism. In the above studies, the authors [37, 39] were able to correct the sodium of most, though not all, of their patients with saline. Moro et al. [39] noted that 74 % of the hyponatremic patients corrected with saline infusions, but the rest required prolonged saline due to massive natriuresis. These patients were given hydrocortisone that reduced the sodium excretion and corrected the hyponatremia. Because of insufficient data, these authors were not able to elucidate the exact cause of the hyponatremia, though the pattern in some suggests CSWS. Whether SIADH or hypothalamic dysfunction leading to dysregulation of

Table 1.4 Studies of heart failure patients with hyponatremia

Heart Failure				
Study	Sodium	Frequency (%)	Sample Size	Study Type
OPTIMIZE-HF [42]	<135	20	48,612	R
OPTIME-CHF [43]	132–135	27	949	R/P
ESCAPE [44]	≤134	24	433	RCT
ACTIV in CHF [45]	<136	21	319	RCT

R retrospective study, *R/P* retrospective analysis of a prospective study, *RCT* randomized control trial

ADH secretion is at play is unclear, but other factors such as brain natriuretic peptide have been suggested to play a part in the desalination process. This still requires further investigation to elucidate the actual incidence of SIADH, CSWS, and hypopituitarism in TBI.

Adverse outcomes and long-term sequela are of concern in patients with intracranial insults. The presence of hyponatremia has been associated with a worse outcome [39], though others [38] have not seen such an association.

Heart Failure

Now classic studies from the 1980s highlighted the importance of hyponatremia in patients with congestive heart failure (CHF) [40]. It was noted that the presence of hyponatremia predicted increased mortality. Further, if treatment of heart failure resulted in a normalization of hyponatremia, mortality was improved [41]. More recent studies have further defined the incidence and significance of hyponatremia in heart failure.

Hyponatremia is seen in one-fifth to one-third of heart failure patients as reported in several large studies (see Table 1.4). In the OPTIMIZE-HF [42] study, about half of the patients had left ventricular systolic dysfunction, and the hyponatremic patients had a lower admission systolic blood pressure and atrial arrhythmias. In the OPTIME-CHF [43] study, the hyponatremic group had more severe heart failure with higher blood urea nitrogen (BUN) and a lower systolic blood pressure. In the ESCAPE Trial [44], a randomized control study of patients with a New York Heart Association class IV due to systolic dysfunction, 69 % of the hyponatremic patients had persistent hyponatremia at discharge. The group with persistent hyponatremia had lower baseline systolic blood pressure, higher serum urea nitrogen (SUN), and was more likely to be treated with spironolactone at baseline and receive larger doses of diuretics during their hospitalization.

Mortality is already high in heart failure patients, and the in-hospital mortality (~6 %) for the hyponatremic group is two to six times higher compared to the normonatremic group [42, 43]. The 60-day mortality was also higher in the hyponatremic patients (16 % vs. 6.4 %) [43]. As expected, those who corrected

their hyponatremia (serum sodium >135 mEq/L) at discharge had a lower 60-day mortality of 11 % compared to those that remained hyponatremic at discharge (17 %). Similarly, in the ESCAPE Trial, those with persistent hyponatremia had a twofold increase in 6-month all-cause mortality (31 % vs. 16 %). These studies are consistent with the thesis that correction of hyponatremia associated with improved heart failure confers a mortality benefit. Unfortunately, the improvement of the hyponatremia per se does not improve outcome [45] as the ACTIV in CHF trial demonstrated no significant difference in 60-day mortality or worsening heart failure between the vasopressin V2 Receptor antagonist groups and the placebo group.

Cirrhosis

Many cirrhotic patients have hyponatremia as demonstrated by a large population study performed by Angeli et al. [46]. They prospectively collected data on 997 cirrhotic patients in Europe, North and South America and Asia for 28 days in hospital and clinic settings in which inpatients accounted for about a half (53 %) of the study population. Mild hyponatremia (serum sodium of ≤135 mmol/L) was seen in 49 % of all the patients, and moderate hyponatremia (serum sodium of ≤130 mmol/L) was found in 28 % of inpatients (vs. 14 % of outpatients). Similar results were seen using these same levels of hyponatremia by Borroni et al. [47] (30 % of 156 consecutive cirrhotic patient admissions) and Porcel et al. [48] (35 % of 155 prospectively studied inpatients). In 126 consecutive ICU admissions, 29 % of critically ill cirrhotic patients had serum sodium of ≤130 mmol/L [49]. Angeli et al. [46] reported a frequency of 5.7 % for more severe hyponatremia (serum sodium ≤125 mmol/L), and only 1.2 % of the inpatient population had a serum sodium ≤120 mmol/L.

Various studies reveal that cirrhotic patients with hyponatremia have a higher frequency of hepatic encephalopathy, spontaneous bacterial peritonitis, hepatorenal syndrome, higher illness severity scores, sepsis, renal failure, and in-hospital mortality compared to normonatremic patients [46, 48, 49]. Borroni et al. [47] showed a death rate of 27 % in patients with a serum sodium ≤130 mmol/L (vs. 9 % in those that were normonatremic) and an even higher mortality of 48 % if the sodium was <125 mmol/L.

Infectious Diseases

Hyponatremia is common in infectious diseases such as HIV/AIDS, pneumonia, meningitis, and malaria. In a prospective study for a 3-month period [50] in patients with AIDS or AIDS-related complex, hyponatremia (serum sodium <135 mmol/L) was present in 38 % of their 167 hospitalized patients. The patients with

hyponatremia on admission were euvolemic (46 %) or hypovolemic (43 %) but most that developed hyponatremia after hospitalization were euvolemic (68 %) and had features consistent with SIADH. Pulmonary infections were the most common cause of SIADH with 93 % of the pulmonary infections due to *Pneumocystis carinii*. Cusano et al. [51] found similar results: one-third (31 %) had a serum sodium $\leq$130 mmol/L but in this study, most patients were hypovolemic (88 %). They noted that those with hyponatremia had a higher frequency of opportunistic infections, with 70 % having *Pneumocystis carinii* infection, almost three times higher than in the normonatremic group; cytomegalovirus infection was also more commonly found. A retrospective analysis of 71 hospitalized patients [52] found a serum sodium <133 mmol/L in half (52 %) of the patients, which was confirmed in a prospective portion of the study with 48 total patients. Again, *Pneumocystis carinii* pneumonia was found in 71 % of patients. Detailed studies in a subset of patients, including ADH levels, suggested SIADH in 15 of 16 patients. Dao et al. [53] reported a sodium <135 mmol/L in about half (46 %) of 661 consecutive women starting antiretroviral therapy in sub-Sahara, but it was not independently associated with mortality though other studies have reported about a twofold increase in mortality associated with hyponatremia compared to normonatremic patients [50, 51].

Community-acquired pneumonia (CAP) is associated with hyponatremia. A retrospective study found hyponatremia in 28 % of patients with CAP [54]. However, two prospective studies place the incidence closer to 10 % [54, 55]. Interestingly, hyponatremia (serum sodium <130 mmol/L) was more frequent in patients with legionella pneumonia at a rate of 29 % (vs. 6.5 % in those with CAP due to other organisms combined) [56].

Brouwer et al. [57] examined hyponatremia in community-acquired bacterial meningitis. A serum sodium <135 mmol/L was present in one-third (30 %) of admissions of 696 adults in this prospective study, but only 6 % had a serum sodium <130 mmol/L. The frequency of hyponatremia varied with a given organism; 33 % in pneumococcal meningitis, 21 % in meningococcal meningitis but unexpectedly high (73 %) in *Listeria monocytogenes* meningitis. In most cases (79 %), the hyponatremia resolved within 3 days, and it was not associated with adverse outcomes or increase in symptoms or complications. The etiology was not determined in this study.

Hanson et al. [58] evaluated 171 consecutive patients in Bangladesh for hyponatremia in severe malaria. On admission, more than half (57 %) of the patients had a plasma sodium <135 mmol/L, and one-third (30 %) had a plasma sodium of <130 mmol/L. The overall mortality rate was 40 %, but the patients that survived actually had lower admission plasma sodium compared to the 69 patients that died. This paradoxical benefit can be explained by a better conscious level (exhibited by a higher Glasgow Coma Scale) in those that survived and therefore continued to take in fluids and subsequently developed hyponatremia. They also noted that hyponatremia improved after crystalloid infusion, suggesting that hypovolemia, not SIADH, was the etiology.

Cancer-Related Hyponatremia

Doshi et al. [59] reported on a large retrospective study including 3,357 patients with cancer admitted to University of Texas M.D. Anderson Cancer Center and noted a serum sodium <135 mEq/L in about half (47 %) of the hospitalized patients (half on admission and a half after hospitalization). The hyponatremia was mild (serum sodium 130–134 mEq/L) in 36 %, moderate (serum sodium 120–129 mEq/L) in 10 %, and severe (serum sodium <120 mEq/L) in 1 % of the patients. Hematologic malignancies tended to have mild hyponatremia whereas patients with head-and-neck and gastrointestinal malignancies had more moderate to severe hyponatremia. Similar findings were reported in smaller retrospective studies [11, 60] but in a prospective study, Berghmans et al. [61] showed the incidence of hyponatremia (serum sodium ≤130 mEq/L) in a cancer hospital setting to be 3.7 %. Hyponatremia was found in all types of cancers with about one-third of the cases attributed to SIADH, another third to volume depletion, and the rest due to a variety of causes.

SIADH is a known cause of hyponatremia in cancer and has been more frequently observed in patients with lung cancers, occurring in about 10–15 % of the cases [62, 63]. Recently, several authors have speculated that atrial natriuretic peptide (ANP) could contribute to the development of hyponatremia in those with lung malignancy, but this was not confirmed by Johnson et al. [64] who investigated this question in a prospective study of 146 patients (22 % of whom had hyponatremia) with small cell lung cancer and nonsmall cell lung cancer.

Patients with malignancy have a high mortality rate, and hyponatremia has been associated as a possible risk factor. Two studies [59, 61] found that patients with hyponatremia had a threefold higher mortality rate and the hazard ratio for 90-day mortality worsens with more severe hyponatremia [59]. Hansen et al. [60] reported a median survival of 7.1 months for the hyponatremic patients compared to 11.2 months for those with normal sodium.

SIADH

SIADH is a common cause of hyponatremia, but the exact prevalence of SIADH is unclear as it is seen in a variety of clinical scenarios, illnesses, and associated with different medications. The diagnosis of SIADH can also be challenging due to the prerequisites needed to make the diagnosis. Volume status is difficult to measure and many times there is more than one possible cause of hyponatremia. Further, SIADH also has a similar biochemical and clinical profile to CSWS. SIADH is common in a variety of pathologies (like lung and CNS) and in hospitalized patients with a range from 2 % to 50 % of hyponatremic cases [23, 27, 38, 61, 65, 66] . It has also been reported with a number of drugs such as SSRI's and MDMA (3, 4-Methylenedioxymethamphetamine) [31, 67]. Anpalahan [24]

reported a rate of 25 % hyponatremic cases with half (51 %) of those cases attributed to SIADH. Nine cases had no apparent cause for SIADH and were presumed to be idiopathic SIADH. Of these, eight were older than 80 years old. The rest of the SIADH cases were thought to be due to some CNS or malignant cause or drug induced.

Cerebral salt wasting or renal salt wasting shares some features with SIADH. As mentioned, CSWS may be seen with CNS disease especially trauma or surgery. However, the true incidence of this entity has been a matter of debate and is discussed further in Chap. 4.

Psychiatric Diseases/Psychogenic Polydipsia

Hyponatremia in patients with psychosis is often multifactorial and is discussed in Chap. 9. Many of these patients have excessive water intake (psychogenic polydipsia) but given the large capacity of the normal kidney to excrete free water, polydipsia alone is not generally the only factor present. Psychogenic polydipsia itself is poorly understood, and the exact incidence is unknown. Some have suggested that polydipsia may be higher than 20 % in chronic psychiatric inpatients with 1–5 % developing symptoms of water intoxication [65]. A cross-sectional survey on 353 psychiatric inpatients [68] found a prevalence of polydipsia of 13 % in the chronic psychiatric inpatient population and 2.4 % of those patients had well-documented episodes of water intoxication. Forty-two percent of the polydipsic patients carried a diagnosis of schizophrenia. The sodium levels at the time of water intoxication ranged from 106 to 114 mmol/L with symptoms of vomiting, confusion, convulsion, and hypotonic coma. Notably, a third of these patients were considered at risk for water intoxication as they had a previous recorded episode of hyponatremia (sodium level $<$135 mmol/L).

Jose and Perez-Cruet [69] surveyed 239 patients in long-term psychiatric ward and noted that 16 (6.6 %) patients had a consistent history of compulsive water drinking (polydipsia) with half of these patients showing symptoms of water intoxication, mainly seizures. The serum sodium ranged between 110 and 131 mEq/L with most of the patients having a diagnosis of schizophrenia. Hariprasad et al. [70] evaluated 20 chronic polydipsic patients with hyponatremia in a psychiatric ward and found results consistent with reset osmostat. (As discussed in Chap. 2, some consider reset osmostat a subtype of SIADH but as discussed in Chap. 4, some consider this a separate entity.)

These studies show that hyponatremia is not rare in chronic psychiatric inpatients and is associated with excessive water intake but in the presence of SIADH and/or reset osmostat. Though antipsychotic medications can cause SIADH and hyponatremia, polydipsia has been curtailed in these schizophrenic patients with medical treatment of the schizophrenia [70].

Endocrine

Endocrine abnormalities are an infrequent cause of hyponatremia. A large retrospective study [71] examined the laboratory records of 15,080 patients in a large hospital and noted that 5.2 % of patients had a serum sodium <135 mmol/L. Hypothyroidism was found more frequently in the hyponatremic group compared to the normonatremic group (4.7 % vs. 1.7 %, respectively). This is similar to what others have shown in the HIV population [52]. Thus, although hypothyroidism is found in hyponatremic patients, a causal relationship is not shown in these studies.

Adrenal insufficiency is also seen within hyponatremic patients, but there a few studies that report on hyponatremia and adrenal insufficiency per se [50, 51]. The finding may be incidental and not clinically evident in some cases [52]. In patients with AIDS or AIDS-related hyponatremia attributed to adrenal insufficiency accounted for less than 5 % of the cases [72].

Exercise-Associated Hyponatremia

Exercise-associated hyponatremia (EAH) is seen in endurance events. Several studies have looked at the prevalence and risk factors leading to EAH. In a study of 488 runners in the 2002 Boston marathon [30], 13 % of the runners had a serum sodium <135 mmol/L with 0.6 % having critical hyponatremia (serum sodium <120 mmol/L). They noted that the hyponatremic group was more likely to have post-race weight higher than the prerace weight in 71 % compared to the normonatremic runners (29 %). Multivariate analysis showed an association of hyponatremia with weight gain, racing time >4 h, and body mass index extremes (which may explain the association with women). Chorley et al. [73] evaluated 96 Houston marathon runners and found an incidence of 22 % of runners with EAH (serum sodium <135 mmol/L). All of the hyponatremic runners were asymptomatic. They also noted that the lower post-race sodium was related to less weight loss during the race and a higher consumption of fluids during the race. Women had a positive fluid balance and less weight loss compared to their male counterparts even though they consumed fluids at a lower rate. In 2003, Reid et al. [74] evaluated 155 runners in a New Zealand marathon and found no incidence of hyponatremia. They noted that the climate was milder, there were fewer aid stations (every 5 km compared to every 1.6 km in many US races), and aggressive hydration was not emphasized.

From these and other studies, a consensus has been reached that certain risk factors could lead to hyponatremia. These include low body weight, female sex, >4 h exercise duration, slow running, race inexperience, excessive drinking behavior and high availability of drinking fluids, altered renal water excretory capacity, and extreme hot or cold environment [75]. This is discussed in more detail in Chap. 10.

Beer Potomania

Beer potomania is a rare cause of hyponatremia mainly due to a low solute intake and binge drinking. Hyponatremia is common in alcoholics and is seen in 5–13 % of these patients admitted to the hospital [76, 77]. Liver failure is a common cause. A prospective study [77] found that of the 127 patients with adequate information to analyze, only two of the 16 hyponatremic patients had beer potomania.

A literature review by Sanghvi et al. [76] summarized 22 patients with mild neurological symptoms (typically confusion) on presentation with mean serum sodium of 108 mEq/L due to beer potomania. They reported a high rate of severe complications (36 %) due to overcorrection with half developing osmotic demyelination syndrome and the other half died. Some of these patients had an overcorrection due to solute administration in the form of either empiric antibiotic administration or saline infusion and subsequent polyuria. Interestingly, because of volume depletion, some of the patients did not have the expected low urine osmolality on admission which made accurate diagnosis challenging.

Beer potomania is rare in this population but it is, nevertheless, seen and subject to a high degree of adverse outcomes. The physician should have a high index of suspicion in this chronic alcoholic population as it is at risk for complications.

Medications and Drugs

A great variety of drugs have been implicated with the development of hyponatremia. Within this section, we examine a handful of drugs with a more extensive discussion given in Chap. 6. Diuretics are known to cause hyponatremia, accounting for 15–50 % of the hyponatremic cases. In the study of 1,000 consecutive geriatric admissions [25] cited above, hyponatremia is present in 7 % of the patients with half of the hyponatremic patients receiving diuretics. The serum sodium was lower in the diuretic group compared to the non-diuretic group with individuals taking potassium-sparing diuretics having lower sodium than the others. In a prospective study [66] of 158 hyponatremic patients admitted to an internal medicine ward, 40 (25 %) patients had diuretic-induced hyponatremia. These 40 patients had lower mean sodium than the remaining hyponatremic patients (121.2 ± 7.2 vs. 126.4 ± 4.1 mEq/L). All of these patients were on a thiazide diuretic, which is expected, as thiazides inhibit water excretion but not urinary concentrating ability, and they were older than the other hyponatremic groups. Other studies have similarly reported about one-third of hyponatremia cases are associated with diuretic use [21, 22, 27] which is higher than diuretic use in the controls of about 15 % [21, 27]. These studies show that diuretic-induced hyponatremia is common in the hospitalized/elderly population, especially those treated with thiazide diuretics.

SSRI's are implicated in causing hyponatremia, though the reported frequency varies greatly. Wilkinson et al. [78] reported a retrospective and case control trial in

patients aged 65 and older in an inpatient/outpatient and rehabilitation setting and found hyponatremia (plasma sodium <130 mmol/L) after a median of 13.5 days with an incidence of about 0.5 %. Most (79 %) of the cases occurred within 3 weeks and in all cases within 10 weeks. The majority of cases (71 %) were women compared with controls, but these results were confounded by body weight as the hyponatremic cases tended to have lower body weights. In a prospective, longitudinal analysis [67], hyponatremia (plasma sodium <135 mEq/L) developed in 12 % of the patients aged 63–90 years old after initiation of paroxetine treatment. The mean time to development was 9 days. Most hyponatremic patients experienced mild symptoms including nausea and fatigue and only one patient complained of confusion. They also measured ADH levels and noted that the ADH levels were, inappropriately, not suppressed in the hyponatremic group.

Desmopressin has long been used for the treatment of nocturia. Pooled data from three multicenter phase III trials [79] noted mild hyponatremia (serum sodium 130–134 mmol/L) in 15 % of the patients and moderate hyponatremia (serum sodium <130 mmol/L) in 4.9 % of patients. These hyponatremic patients were older than 65 years old, had lower serum sodium at baseline, higher basal 24-h urine volume per body weight, and had gained weight at the time of the serum sodium nadir. A double-blind study [80] found similar results with 3 % of the population developing moderate hyponatremia (serum sodium <130 mmol/L); most were above age 65. The most serious symptom was headache but most patients were asymptomatic. Hyponatremia has also been reported in children treated with desmopressin. Postmarketing safety data revealed 151 cases of hyponatremia in children where most (145) of the children received intranasal desmopressin and the rest had an oral formulation. Symptoms including headache, nausea, and vomiting were seen in these children [81].

Conclusions

Hyponatremia is a common electrolyte abnormality that is seen in various settings and to varying degree. The impact of hyponatremia is larger with a lower sodium level as it may represent a sicker population or deregulation of the sodium/water homeostasis and make patients more susceptible to complications if it is not corrected or corrected too rapidly.

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Chapter 2
Physiology of Water Balance and Pathophysiology of Hyponatremia

Jeffrey C. Sirota and Tomas Berl

Introduction

The normal function and ultimate survival of every cell in the human body depends on its presence within the proper milieu. The tonicity of the extracellular fluid is a key component of that environment and acts as an important determinant of the intracellular composition as well. Myocyte function, signaling pathways, cell membrane integrity, and neuronal depolarization are just a few examples of crucial aspects of our physiology that depend on the constancy of the ambient osmolarity. As the single most important determinant of extracellular tonicity, the concentration of sodium in the serum must be tightly regulated for these myriad cellular processes to be discharged normally. Correspondingly, significant deviations in the serum sodium concentration are tolerated poorly and result in cellular dysfunction. The stability of the serum sodium concentration within a narrow range despite wide variations in water intake, solute ingestion, and non-urinary water losses is the result of a strict balance between water intake and water output. This balance is achieved primarily through regulation of urinary tonicity. When these balance mechanisms are disrupted or overwhelmed, dysnatremias ensue.

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Physiology of Water Balance

Concept of Water Balance and Its Relationship to Serum Sodium Concentration

Central to the understanding of the serum sodium concentration and its regulation is the concept of *effective osmolarity*. An effective osmole is a species in the aqueous phase of the plasma that does not readily penetrate cell membranes and therefore acts to hold water within the extracellular space. By this description, a membrane-impermeable molecule like glucose is an effective osmole while a molecule with free membrane permeability such as urea would be considered an ineffective osmole. (It must be noted that while there is some delay in equilibration of urea across various compartments, it is a highly permeable molecule and in steady state should be considered an ineffective solute.). While a variety of species contribute to the overall effective plasma osmolarity, sodium is by far the most important. In fact, sodium salts account for more than 95 % of the effective osmoles under normal circumstances, and the effective plasma osmolarity (P_{osm}) can therefore be estimated with the following simple equation:

$$\text{Effective } P_{osm} \cong 2 \times \text{Plasma sodium concentration.} \tag{2.1}$$

This relationship means that the plasma sodium concentration accurately reflects the plasma osmolarity in the vast majority of clinical situations, and therefore, overall body osmoregulation relies primarily upon the regulation of plasma sodium concentration.

As a result, further understanding of disorders of osmolarity relies on a clear understanding of the definition of the sodium concentration. In that regard, expansion of the plasma osmolarity definition is helpful. Because of the osmotic equilibrium between the intracellular and extracellular compartments, the effective P_{osm} is equal to the effective osmolarity throughout the entire total body water, regardless of compartment:

$$\text{Effective } P_{osm} = \text{Effective osmolarity of the total body water.} \tag{2.2}$$

The effective osmolarity of the total body water is the ratio between the total body's effective solutes and the total body water, so therefore:

$$\text{Effective } P_{osm} = \frac{\text{Effective extracellular solutes} + \text{Effective intracellular solute}}{\text{Total body water}}. \tag{2.3}$$

Because the chief effective extracellular solute is exchangeable sodium and the chief effective intracellular solute is exchangeable potassium (where

"exchangeable" refers to the store of ions unbound and free for exchange between compartments), Eq. (2.3) can be reapproximated in the following way:

$$\text{Effective } P_{\text{osm}} = \frac{(2 \times \text{exchangeable sodium}) + (2 \times \text{exchangeable potassium})}{\text{Total body water}}, \tag{2.4}$$

where the 2 multiplier accounts for the accompanying anions. Substituting (2.1) into (2.4) yields the following [1]:

$$\text{Plasma sodium concentration} \cong \frac{\text{Exchangeable sodium} + \text{Exchangeable potassium}}{\text{Total body water}}. \tag{2.5}$$

Considering these determinants of the plasma sodium concentration allows for a conceptual framework for understanding disorders of sodium concentration. The total body sodium is regulated by mechanisms designed to preserve intravascular volume, blood pressure, and tissue perfusion; these regulatory mechanisms do *not* target any specific osmolarity or sodium concentration. Instead, the maintenance of a stable serum sodium concentration is accomplished chiefly through regulation of total body water, the denominator of (2.5). A variety of mechanisms act through the kidney to regulate total body water content so that changes in total body water match changes in exchangeable sodium and potassium, thereby producing a stable serum sodium concentration despite any possible variations in the absolute amounts of solute present.

Given the importance of total body water regulation, the balance between water intake and excretion must be strictly maintained. As such, this concept of water balance is absolutely essential to an understanding of hyponatremia (as well as hypernatremia). As described in detail below, the regulation of water intake is accomplished largely through control of thirst, while water excretion is regulated chiefly through urinary dilution and concentration as warranted by the demands of the clinical setting. It follows that abnormalities in water balance are responsible for the dysnatremias, and with respect to hyponatremia, this fundamental concept means that *all cases of hypotonic hyponatremia reflect either absolute or relative positive water balance*. Put another way, hyponatremia supervenes when the intake of water exceeds the kidney's ability to excrete sufficiently dilute urine. Relative water retention most often arises when urinary diluting mechanisms are disturbed, but it can also occur when urinary dilution is intact.

A full understanding of the pathogenesis of hyponatremia in light of water balance considerations requires attention to both sides of the water balance equation. On the output side, the body loses roughly 1,100 mL of water per day from stool (200 mL) and from evaporation at skin (500 mL) and respiratory tract surfaces (400 mL) [1]. In addition, there is a minimum amount of water that the kidney must excrete as part of the process of solute clearance. To maintain electrolyte balance, an individual ingesting a typical North American diet must excrete a total of

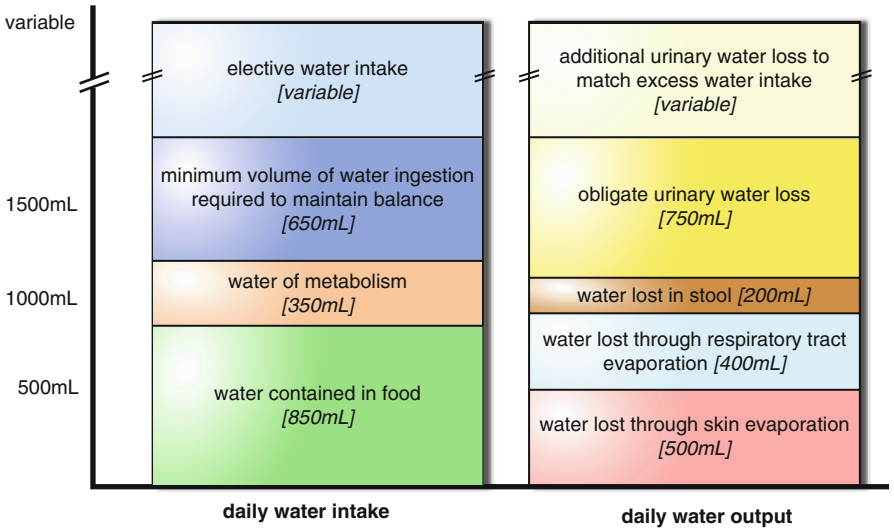

Fig. 2.1 Cumulative daily water balance. The values shown above assume normal skin, respiratory tract, and stool losses (i.e., an absence of excessive sweating, tachypnea, mechanical ventilation, and diarrhea). In addition, the volume of obligate urinary water loss is based on calculations of an 80-kg subject consuming a standard North American diet who has normal urinary concentrating ability, as described in the text

400 mOsm of consumed electrolytes (comprised primarily of sodium, potassium, and their accompanying anions). Additionally, roughly 500 mOsm of urea must be excreted each day—100 mOsm produced by normal catabolism plus 400 mOsm from dietary protein metabolism (every gram of ingested protein yields 5 mOsm of urea, an 80 kg person consuming 1 g protein per kilogram of body weight produces 80 g $\times$ 5 mOsm $=$ 400 mOsm of urea). With a maximum urinary concentration of 1,200 mOsm/L, these 900 mOsm of solute can be excreted in a minimum of 750 mL of water. Therefore, in total, a minimum of 1,850 mL of water is lost per day by the average size person on a North American diet (Fig. 2.1).

On the intake side, there are three principal components to consider—water ingested in liquids, water consumed in solid foods, and water produced by metabolism. Water input from ingested food and metabolism is relatively fixed at about 1,200 mL per day, closely matching the fixed non-urinary losses [1] (Fig. 2.1). Therefore, to stay in balance and match the minimum output of 1,850 mL, a minimum of 650 mL of water must be ingested each day, which roughly matches the obligate urinary water losses. When that precise amount of fluid is ingested, water balance is easily maintained. However, the kidney has evolved a remarkable ability to vary the tonicity of urine so that balance is maintained in the setting of wide variations of intake and non-renal water losses. When any amount of fluid in excess of the 650 mL is ingested (which is common due to normal drinking habits dictated by social norms), the additional free water is excreted through dilution of the urine. Conversely, when an individual drinking the average 2 L of fluid per day

develops increased water losses above normal (from diarrhea, sweating, increased respiratory losses, etc.), balance is maintained through concentration of the urine as well as the stimulation of thirst in order to increase fluid intake. Any significant disturbances in these processes of matching water intake to output will result in dysnatremias. Because urinary tonicity regulation is key in the maintenance of water balance, a more precise and quantitative understanding of urinary free water clearance is warranted.

A Quantitative Approach to Water Clearance

Conceptually, it can be useful to consider any given volume of urine as comprised of two separate components. First, all solutes cleared by the kidney can be thought of as being excreted in a urinary component whose concentration is isotonic to the plasma. This isotonic solute clearance (C_{osm}) is excreted in combination with a second urinary component, the clearance of water (C_{water}). These two clearances comprise the total urine volume flow (V), such that

$$V = C_{osm} + C_{water}. \tag{2.6}$$

The first component, C_{osm}, can be viewed as a nonregulated quantity, determined exclusively by the clearance demands created by the individual's solute intake. Water clearance, on the other hand, is highly regulated in order to achieve the necessary water balance, primarily through the actions of the pituitary hormone arginine vasopressin (AVP).

Since water balance is crucial to regulation of plasma osmolarity, further exploration of the C_{water} term is essential for understanding disorders of plasma osmolarity. The clearance of any substance is equal to the product of urine flow and the ratio of its urinary concentration to its plasma concentration:

$$C_x = V \times \left(\frac{U_x}{P_x}\right). \tag{2.7}$$

Substituting this definition for C_{osm} into the urine flow equation (2.6) yields the following:

$$V = \left[V \times \left(\frac{U_{osm}}{P_{osm}}\right)\right] + C_{water}, \tag{2.8}$$

where U_{osm} is the urine osmolarity and P_{osm} is the plasma osmolarity. This relationship can be further rearranged to the following:

$$C_{water} = V \times \left(1 - \frac{U_{osm}}{P_{osm}}\right). \tag{2.9}$$

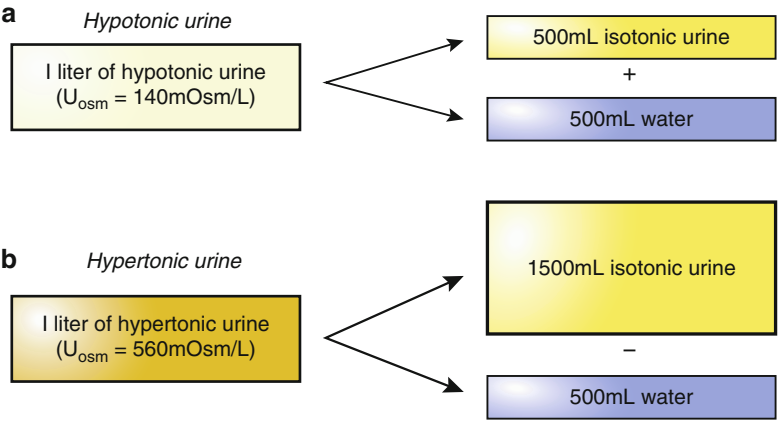

Fig. 2.2 Positive and negative water clearance. Panel (**a**) shows 1 L of hypotonic urine (U_{osm} = 140 mOsm/L) conceptualized as the sum of 500 mL of isotonic urine and 500 mL of water. This is an example of positive water clearance, in which free water is lost from the body. Panel (**b**) shows 1 L of hypertonic urine (U_{osm} = 560 mOsm/L) conceptualized as 1,500 mL of isotonic urine with 500 mL of water removed. This is an example of negative water clearance, in which free water is retained through absorption. Both panels assume a plasma osmolarity of 280 mOsm/L

From this equation, it is evident that when U_{osm} is less than P_{osm}, the urine is hypotonic and free water excretion is positive. Conversely, when U_{osm} exceeds P_{osm}, the urine is concentrated above plasma, and free water excretion is negative.

To illustrate this concept, consider a situation in which the urine is hypotonic compared to the plasma (i.e., $U_{osm} < P_{osm}$). If a patient with a plasma osmolarity of 280 mOsm/L excretes a liter of urine with an osmolarity of 140 mOsm/L, then the free water clearance using (2.9) above would be +500 mL ($C_{water} = 1\text{ L} \times (1 - (140\text{ mOsm/L}/280\text{ mOsm/L})) = 0.5\text{ L}$). This liter of urine can therefore be conceptualized as 500 mL of isotonic urine and 500 mL of water. The positivity of the free water clearance value indicates that this excretion of urine has produced a net loss of water from the body.

Conversely, if the same patient excretes a liter of hypertonic urine with an osmolarity of 560 mOsm/L, then the free water clearance would be –500 mL ($C_{water} = 1\text{ L} \times (1 - (560\text{ mOsm/L}/280\text{ mOsm/L})) = -0.5\text{ L}$). Conceptually, this liter of urine can be viewed as 1.5 L of isotonic saline with 500 mL of water removed. This negative water clearance corresponds to water reabsorption in the kidney, producing hypertonic urine and the net retention of water. Figure 2.2 illustrates these concepts.

It is important to recognize that both of the osmolarity terms in (2.9) include the contribution of urea, but because urea is an ineffective osmole due to its cell membrane permeability. A more clinically useful tool that excludes urea is the electrolyte free water clearance, which better predicts directional changes in serum sodium concentration. This term, the *electrolyte-free water clearance* (C^{e}_{water}), is defined by the following equation: [2]

$$C^{e}_{water} = V \times \left(1 - \frac{U_{Na} + U_{K}}{P_{Na}}\right). \quad (2.10)$$

From (2.10), it follows that a positive electrolyte-free water clearance occurs when the plasma sodium concentration exceeds the sum of urinary sodium and potassium concentrations. In such a setting, the urine is hypotonic relative to plasma (even if its total tonicity is greater than that of plasma), and if the urinary losses are not matched by appropriate hypotonic water intake, then the resultant negative free water balance causes an increase in the serum sodium concentration. Conversely, when the urinary concentrations of sodium and potassium exceed the serum sodium concentration, then the electrolyte-free water clearance becomes negative, reflecting the reabsorption of free water. This setting results in the excretion of hypertonic urine, and the kidney's reabsorption of free water will decrease the serum sodium concentration.

Because hypotonic hyponatremia is *always* the result of relative water retention, the assessment of a hyponatremic patient's electrolyte-free water clearance using the above equation can be very useful in determining the kidney's role in the positive water balance. Very often, this approach will reveal a defect in urinary dilution as the cause of the hyponatremia. Alternatively, it may reveal appropriate urinary dilution, suggesting a different underlying cause of the hyponatremia.

Given the overall importance of the urinary diluting mechanism in preventing water retention, consideration of the nephron's various transport mechanisms and their hormonal control is essential in the understanding of the pathogenesis of hyponatremia. These specialized mechanisms throughout the nephron will be addressed below in sequential order and illustrated in Fig. 2.3.

Components of the Urinary Diluting and Concentrating Mechanisms

Glomerular Filtration and the Proximal Convoluted Tubule

Fine control over water balance occurs in the distal nephron, and as a result, adequate delivery of tubular fluid to that nephron segment is essential in allowing this tight regulation to occur. Under normal conditions, 70 % of the glomerular filtrate is reabsorbed isotonically through the water-permeable proximal convoluted tubular epithelia. The remaining 30 % of the isotonic filtrate is essential to the loop of Henle's generation of a medullary interstitial tonicity gradient, which is ultimately required for distal water balance control. Because of the importance of this medullary tonicity gradient in the overall control of water balance (particularly in the process of urinary concentration), decreases in the amount of fluid leaving the proximal tubule can interfere with water balance regulation by preventing the proper establishment of the tonicity gradient. In addition, decreased tubular flow

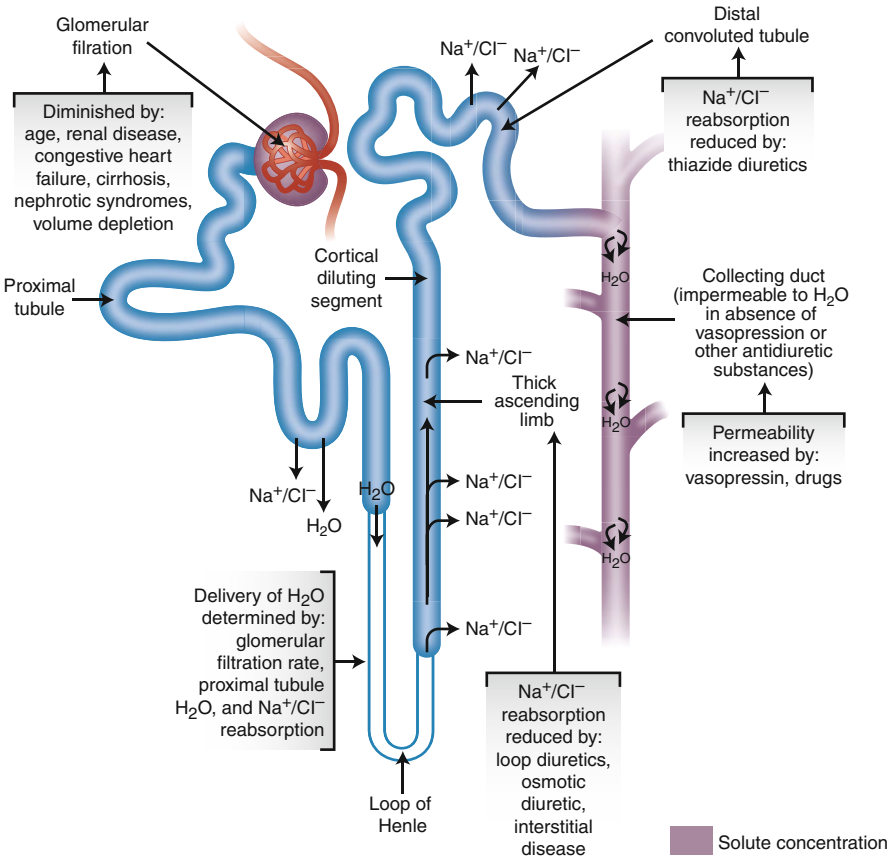

Fig. 2.3 Mechanisms of urinary dilution. The specialized mechanisms in each nephron segment that contribute to urinary dilution are shown, as well as the sites of impairment in urinary dilution that produce hyponatremia

can deprive the distal nephron of the substrate it needs to exert control over water balance and sets the upper limit of urine flow that can be excreted. These states of poor distal delivery can arise when the glomerular filtration rate (GFR) is decreased or proximal tubular reabsorption is increased; this combination is often seen in the setting of volume depletion or poor renal perfusion.

The Loop of Henle

As isotonic filtrate moves through the descending thin limb of the loop of Henle, water is reabsorbed through the aquaporin-1 water channel, causing progressive concentration of tubular fluid [3]. The degree to which the increase in the tonicity of

tubular fluid is contributed to by solute addition seems variable among species, but a component of urea addition probably also contributes to the process. Water reabsorption in this nephron segment is passive, driven by the increased medullary hypertonicity that results largely from high urea levels (which, in turn, result from inner medullary collecting duct urea reabsorption). Tubular fluid reaches its peak osmolarity of approximately 1,200 mOsm/L at the loop's hairpin turn, after which the concentrated tubular fluid begins its ascent through the water-impermeable thick ascending limb. Sodium reabsorption is probably passive in the thin ascending limb, but in the thick ascending limb, tubular fluid sodium, chloride, and potassium are reabsorbed through $Na^+/K^+/2Cl^-$ cotransporters, while water remains in the tubular lumen. This process results in progressive dilution of the tubular fluid, until an osmolarity nadir is reached as the fluid enters the distal tubule with a tonicity of about 100 mOsm/L.

In addition to diluting the tubular fluid, solute reabsorption and water impermeability throughout the ascending limb also create a gradient of interstitial tonicity throughout the medulla, with increasingly higher tonicities at deeper levels of the medulla. This gradient is absolutely essential in the more distal and fine control over water balance exerted by AVP. Substantial decreases in the delivery of fluid to the loop of Henle due to low glomerular filtration rate (GFR) or increased proximal tubular reabsorption can impair the kidney's concentrating ability because this ability relies upon the ascending limb's ability to generate this medullary osmolarity gradient. In addition, the medullary hypertonicity gradient depends upon regulated blood flow through the hairpin configuration of the vasa rectae that supply the area [4]. Significant increases in the flow of blood through these vessels can partially dissipate the tonicity gradient and thereby diminish more distal water reabsorption.

The Distal Tubule and Collecting Duct

The delivery of hypoosmotic fluid to the collecting duct and the descent of the collecting duct through a progressively more hypertonic medullary interstitium provide a background in which fine control over water excretion can be exerted. At this point, the major determinant of urine osmolarity and water clearance is arginine vasopressin (AVP), a cyclic hexapeptide with an additional three amino acids, synthesized in the supraoptic and paraventricular magnocellular nuclei of the hypothalamus. Understanding the regulation and action of this hormone is vital for understanding the physiology of water balance and the pathophysiology of most hyponatremic states.

AVP is synthesized in the hypothalamus and stored in posterior pituitary secretory granules until its release is prompted by either osmotic or non-osmotic stimuli. The osmotic trigger for AVP release is mediated by osmoreceptor cells located in the organum vasculosum of the lamina terminalis and the subfornical organ. These cells sense ECF osmolarity through cellular swelling, and via their projections to the anterior hypothalamus and through activation of TRV4 channels, they trigger AVP

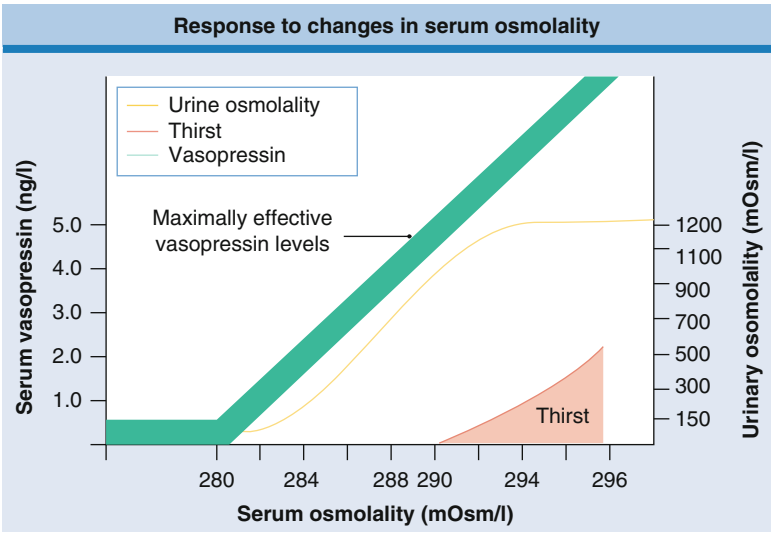

Fig. 2.4 Vasopressin levels, urinary osmolarity, and thirst at different serum osmolarities. The levels of vasopressin, urinary osmolarity, and thirst are shown in relationship to serum osmolarity. (Adapted from Narins RG, Krishna GC. Disorders of water balance. In: Stein JH, editors. Internal medicine. Boston: Little, Brown; 1987, with permission from Elsevier)

release in response to an increase in ECF osmolarity of as little as 1 %. In contrast, a 1 % decrease in ECF osmolarity results in complete AVP suppression. In absolute terms, the window for AVP release is normally set between 280 and 290 mOsm/kg (Fig. 2.4). In light of the relationship between serum sodium concentration and osmolarity, this osmotic set point for AVP release results in non-detectable plasma AVP levels when the serum sodium concentration is below 135 mEq/L, and AVP levels reach approximately 5 pg/mL when the serum sodium concentration is 140 mEq/L. Working properly, this system confines plasma osmolarity and serum sodium concentration to a very narrow range.

More important in the consideration of hyponatremic states are the variety of non-osmotic stimuli for AVP release, the most important of which is decreased blood pressure or intravascular volume. Venous baroreceptors in the atria and arterial baroreceptors in the carotid arteries and aorta detect intravascular volume and blood pressure. In concert, these receptors will prompt AVP release when they perceive a decrease in blood volume or pressure, sending afferent signals to the brain through the vagus and glossopharyngeal nerves. The degree of decrement in intravascular volume or pressure that stimulates AVP release has been reported to be approximately 7 %. Because this stimulus for AVP release is involved in the defense against circulatory collapse, it is considerably stronger than the osmotic signals and will therefore prevail over any contradictory osmotic signals that may coexist. This discrepancy in the stimulus strength is of considerable importance when considering certain hyponatremic states, as described in the next section. It is also important to note that a variety of other non-osmotic stimuli for AVP release exist as well, including nausea, hypoglycemia, pain, and emotional stress.

Regardless of the source of its stimulation for release, circulating AVP exerts its influence over water balance in the collecting duct of the kidney. In the absence of AVP, the collecting duct is largely water impermeable, and thus, the hypotonic fluid that reaches the collecting duct will be excreted without significant tonicity changes as dilute urine. In the presence of AVP, however, urine tonicity will change dramatically. AVP binds to the V2 receptors on the basolateral membrane of collecting duct principal cells, resulting in translocation of aquaporin-2 (AQP2) water channels into the luminal membranes through a cyclic AMP signaling pathway [5, 6]. The resulting increased water permeability of the collecting duct causes passive water reabsorption down its concentration gradient into the hypertonic medullary interstitium. AVP's effect on collecting duct water permeability through this mechanism occurs within minutes and allows for rapid and short-term regulation of water clearance. However, it is also notable that when elevations in plasma AVP levels are sustained for longer than 24 h, the expression of AQP2 is increased, and the greater number of AQP2 channels available for translocation into the luminal membrane allow for even greater maximal water permeability in the collecting duct. This long-term regulation has been observed and likely has clinical relevance in the hyponatremias that can accompany the edematous disorders.

Through its short-term action on the water permeability of the collecting duct, AVP will decrease urinary free water clearance until the stimulus for its release from the pituitary is removed. Feedback cessation of AVP stimulation can occur when an osmotic stimulus is extinguished as a result of AVP-stimulated water reabsorption which will dilute a high serum sodium concentration and return serum osmolarity to the normal range. Feedback in this system can also occur if water reabsorption improves any decreases in intravascular volume or pressure that may have caused a non-osmotic stimulation of AVP release.

Taken together, this feedback system allows for a relatively constant serum sodium concentration despite wide variations in water intake and significant changes in non-renal water losses. Practically speaking, an ingested water load will cause a drop in plasma tonicity that causes inhibition of AVP secretion, leading to a water diuresis that ultimately normalizes the decreased plasma tonicity. Conversely, plasma hypertonicity caused by water deprivation will stimulate AVP secretion, causing an antidiuresis, and the positive water balance and retention will dilute the plasma hypertonicity back to the normal range. The dynamic ability of the kidney to vary the tonicity of urine from roughly 50 mOsm/L to in excess of 1,200 mOsm/L allows accommodation of substantial variability in water intake and non-renal water loss, and this capacity has afforded the species with a tremendous survival advantage and flexibility as it evolved to meet the challenges of life on dry land.

While AVP plays a primary role in determining urine tonicity through its actions in the collecting duct, there also appears to exist an AVP-independent regulation of urinary concentration related to the rate of distal solute delivery. Specifically, urine osmolarity has been shown to decrease as solute excretion increases. This urinary dilution may result from the fact that solute diuresis can cause increased medullary blood flow and therefore decreased medullary hypertonicity, which would in turn blunt the urine concentrating ability of AVP. Secondly, increased solute delivery produces rapid flow in the collecting duct that may not allow complete osmotic

equilibrium to occur between the tubular fluid and interstitium when AVP is present, thereby causing a more dilute urine than the AVP levels should dictate.

As mentioned above, both the input and the output side of water balance must be appreciated in understanding water balance physiology, so in addition to this consideration of renal water excretion, it is important to understand the complex control over water intake that is effected through the regulation of thirst. First and foremost, hypertonicity is known to be a potent stimulus for thirst as well as AVP release. The resultant increase in water intake acts in concert with the antidiuretic effect of AVP to restore normal tonicity. With regard to its role in regulating plasma osmolarity, however, thirst control is less sensitive than AVP regulation and is complicated by a variety of other influences. Thirst stimulation occurs at a plasma tonicity approximately 10 mOsm higher than does osmotic stimulation of AVP release; [7] thus, a 2–3 % increase in plasma osmolarity is required to stimulate thirst, in contrast to the 1 % increase required to stimulate AVP release. In fact, the osmotic set point for thirst stimulation roughly correlates with the point at which urine is maximally concentrated through AVP's action (Fig. 2.4), so increased water intake is prompted only when the kidney's ability to conserve water is nearly at its capacity, thereby serving as a second line of defense against severe hypernatremia. Secondly, thirst is influenced by factors other than osmolarity, such as mouth dryness [8, 9], hypovolemia, hypotension, and angiotensin II. Additionally, thirst can be suppressed by oropharyngeal mechanoreceptors when they detect fluid consumption [10]. Unlike AVP's minute-to-minute control over urinary water excretion, these thirst control mechanisms do not reflect regulation of plasma osmolarity per se but instead exist to prevent overcorrection of hyperosmolarity, as gastrointestinal absorption of ingested water can take up to an hour. The defense against overcorrection is further bolstered by the fact that fluid intake rapidly causes a transient suppression of both thirst and AVP levels, significantly before any resultant drop in plasma tonicity [11, 12].

Taken together, control over thirst and the regulation of urine composition allow for substantial control over water balance despite wide variations in water intake and non-renal fluid losses. Maintaining this stability allows for a relatively constant plasma osmolarity, and conversely, dysnatremias occur when this balance is disrupted. The pathophysiology of the hyponatremic disorders should be understood in light of these balance considerations.

Approach to the Patient with Hyponatremia

Introduction

Hyponatremia develops when water intake exceeds the body's ability to excrete urine that is sufficiently dilute to maintain strict water balance, resulting in net water retention. The underlying cause of the defect in urinary dilution is related

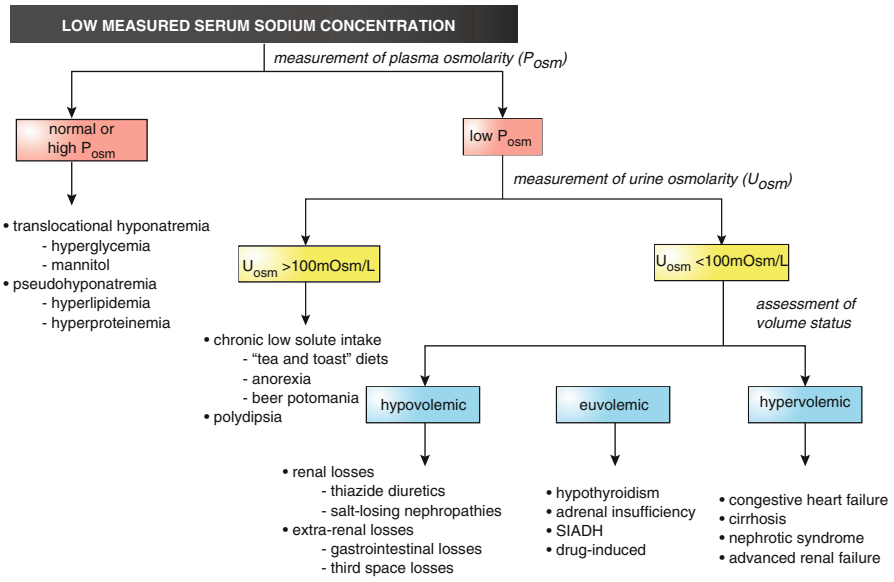

Fig. 2.5 Approach to the patient with hyponatremia. A general and systematic approach to the patient with a low measured serum sodium concentration

either to the secretion of AVP in response to non-osmotic stimuli or, in AVP's absence, to dramatic alterations in water and solute intake that prevent normal water balance from being maintained. A general approach to a low measured plasma sodium measurement is shown in Fig. 2.5.

Defining Hypotonic Hyponatremia

The first step in assessing a patient with a low reported serum sodium concentration is to evaluate whether this laboratory value represents hypotonic hyponatremia. Because sodium is the primary determinant of serum osmolarity [13], true hyponatremia should be hypotonic in nature. However, there are settings in which low serum sodium values can occur in patients with normal or even high plasma osmolality.

The more common of these settings is that of translocational hyponatremia. In this circumstance, abnormally high concentrations of osmotically active particles are present in the serum and draw water from the intracellular compartment to establish osmotic equilibrium. The commonest solutes to cause this shift of water are glucose, mannitol, and glycine (which is often used as an irrigant during hysteroscopy, laparoscopy, or transurethral resection of the prostate or bladder). Hyperglycemia bears particular mention as translocational hyponatremia can be quite common in the setting of diabetic ketoacidosis and hyperosmotic hyperglycemic non-ketotic coma, and up to 20 % of

hospitalized cases of hyponatremia may result from concomitant hyperglycemia [14]. Theoretical calculations previously suggested that for every increase of 100 mg/dL in plasma glucose, the plasma sodium decreases by 1.6 mEq/L [15]. Later experimental work has shown that this is an underestimate; a correction factor of at least 2.4 mEq/L per 100 mg/dL of glucose appears to be more accurate [16].

In addition to these translocational hyponatremias, a phenomenon known as pseudohyponatremia can produce a low measured serum sodium concentration despite the absence of hypotonicity. Flame emission spectrometry assays plasma sodium concentration by quantifying the intensity of emitted light from a specific volume of plasma and translating that intensity into a concentration of sodium per unit volume of plasma. This calculation assumes that 7 % of the plasma volume is comprised of nonaqueous lipid and protein, which is true under normal circumstances. However, when the nonaqueous portion of plasma rises significantly, the measured plasma sodium concentration per unit of total plasma volume will be falsely decreased (although the concentration per unit of plasma water would not be). Pseudohyponatremia of this variety most commonly occurs in the setting of severe hyperlipidemia or hyperproteinemia; these disorders can reduce the aqueous phase of plasma from the usual 93 % of total plasma volume to below 75 % [17, 18]. Of note, the measured plasma osmolarity in this condition will remain normal as a standard osmometer measures the tonicity of only the aqueous phase. Suspicion of pseudohyponatremia can be confirmed through the use of direct reading potentiometry with sodium selective electrodes on an undiluted sample, which will yield the accurate sodium concentration regardless of the proportion of plasma that exists in the nonaqueous phase.

Hypotonic Hyponatremia in the Setting of Dilute Urine

Once it has been verified that hyponatremia is occurring in the setting of plasma hypotonicity, the clinical approach commences with an evaluation of the urine osmolarity. If urine is demonstrated to be dilute (i.e., with an osmolarity of less than 100 mOsm/L), then the differential diagnosis is confined to polydipsia and states of low solute intake.

Polydipsia resulting in hyponatremia is a condition in which water intake exceeds the kidney's ability to excrete a sufficiently dilute urine despite intact diluting capacity. This disorder remains somewhat uncommon in patients with normal renal function because the normal kidney can excrete a volume of free water that is difficult to exceed through ingestion. To illustrate, consider that normally functioning kidneys are capable of achieving a free water clearance equal to roughly 20 % of the GFR. As such, a person with a GFR of 100 mL/min can excrete over 25 L of free water per day. Achieving positive water balance in this setting would then require the subject to ingest over 25 L of water in a day, which is a difficult feat.

However, while ingesting above the kidney's daily water excretion capability is difficult, exceeding the hourly rate of urinary free water clearance is more attainable on a short-term basis. The kidney rarely excretes more than 1 L of water per hour, so excessive water drinking over a short period of time can lead to transient positive water balance. Of course, for the resulting hyponatremia to persist, the excessive water ingestion must be sustained; once it ceases, then the full suppression of AVP release will result in the rapid excretion of the excess free water and the swift resolution of the transient hypoosmolarity.

From the above discussion, it follows that exceeding the kidney's ability to clear free water is easier to achieve when GFR is decreased, as maximum water clearance would be diminished and therefore positive water balance would occur at lower volumes of ingestion. Still, sustained hyponatremia due to polydipsia can occur in patients with normal GFR, albeit rarely. One setting where this disorder is particularly notable is in institutionalized psychiatric patients with schizophrenia [19, 20]. Compulsive water-drinking behavior has been reported in up to 6 % of such patients [21]. It is speculated that some of these patients have a central defect in thirst regulation [22] and may have lower osmotic set points for thirst stimulation than they do for ADH release [23], leading to their excessive water intake.

In these patients, it should be noted that excessive water intake is often only one contributor to the multifactorial hyponatremia. First of all, many patients with schizophrenia are prescribed psychiatric medications that enhance AVP release and stimulate thirst, thereby interfering with appropriate urinary dilution while also stimulating water intake. In addition, patients with schizophrenia have been shown to release AVP during episodes of acute psychosis [24, 25], allowing for positive water balance to occur with less profound polydipsia than would be required otherwise. AVP responsiveness in the kidney also appears to more pronounced in these patients for reasons that are not entirely unclear [26]. Finally, the threshold for AVP release may be reset to a lower osmolarity in patients with schizophrenia.

Aside from the setting of schizophrenia and acute psychosis, polydipsia can result in hyponatremia in other clinical situations as well, although far less commonly. For example, patients with hypothalamic lesions or infiltrative diseases such as sarcoidosis that affect the brain's thirst control center can develop excessive water drinking that produces positive water balance [27].

Another setting in which hypotonic hyponatremia can occur in the face of a dilute urine is in states of prolonged low solute intake. In order to maintain daily balance, the average adult eating a normal diet must excrete roughly 800 mmol of solute per day (as described above), most of which is the result of dietary intake and nutrient metabolism. Assuming that maximally dilute urine has an osmolarity of 50 mOsm/L, these 800 mmol can be excreted in up to 16 L of urine. As such, neutral water balance can be achieved as long as the individual does not ingest over 16 L of water per day. However, in patients with severely low solute intake (e.g., anorectics or those on "tea and toast" diets), the maximum amount of dilute urine that can be excreted will be substantially lower because the obligate solute excretion is decreased. Accordingly, positive water balance can occur with significantly less water ingestion [28].

To illustrate, consider a patient who needs to excrete only 200 mmol of solute per day due to poor oral intake. With a maximally dilute urine of 50 mOsm/L, this patient can produce a maximum of 4 L of urine per day, a volume that is far easier to exceed through ingestion. Due to the extremely low solute content of beer and the high volume of this beverage that some patients consume, this situation can easily occur in when patients subsist on little food and excessive beer. The resulting hyponatremia has been termed beer potomania.

Hypotonic Hyponatremia in the Setting of Non-dilute Urine

Most patients with hypotonic hyponatremia produce urine that is not maximally dilute (i.e., U_{osm} exceeding 100 mOsm/L), and their hyponatremia reflects positive water balance primarily as a consequence of persistent AVP secretion. In some settings, this AVP release is stimulated by decrements in total blood volume. In others, the ECF volume may be expanded, but there is a decrement in *effective* arterial blood volume (EABV) that is involved in the pathogenesis of the hyponatremia.

Because the concept of EABV is central to understanding the pathogenesis of hyponatremia in a variety of conditions, a further explanation is warranted before proceeding. EABV refers to the volume of blood perfusing the peripheral tissues, and maintaining an adequate perfusion relies not just on the intravascular volume but also on cardiac output, peripheral vascular resistance, and oncotic pressure. Depending on the physiology of these other determinants, EABV can be significantly reduced even in the setting of ECF volume expansion. Central to the pathogenesis of hyponatremia in these conditions, diminished EABV can stimulate AVP release in the same way that true volume depletion does. In addition, both types of volume depletion produce alterations in renal hemodynamics that reduce GFR and enhance proximal tubular reabsorption, resulting in diminished delivery of fluid to the distal diluting segments of the nephron and thereby further limiting the volume of urine that can be excreted.

It should be noted that not all cases of hypotonic hyponatremia in the setting of non-dilute urine involve states of low EABV, but many of them do. The general approach to patients with hypotonic hyponatremia and non-dilute urine begins with an assessment of volume status.

Hypovolemic Hyponatremia

Hypovolemic hyponatremia arises when the total body sodium is decreased out of proportion to a decrease in the total body water. In this situation, the relative degree of water retention is responsible for the low serum sodium concentration. The non-osmotic release of AVP triggered by the fall in intravascular volume or pressure overrides the suppressive signals prompted by osmoreceptors that detect

hypoosmolarity. This hierarchy of stimuli reflects what has been termed the "law of the circulating volume," whereby the preservation of volume and defense of blood pressure takes precedence over the maintenance of tonicity.

There are a variety of potential sources of fluid loss that can produce hypovolemic hyponatremia. The concentration of sodium in the urine can suggest whether the fluid loss is renal or extra-renal in nature. In cases of fluid loss through the gastrointestinal tract or into the third space (e.g., in the setting of pancreatitis, bowel obstruction, or burns), the urinary sodium concentration will typically be low (i.e., <20 mEq/L) if renal function is normal, reflecting the sodium avidity that results from increased angiotensin II, aldosterone, and other sodium-retaining neurohumoral pathways. An exception to this low urine sodium is sometimes seen in cases of vomiting, in which metabolic alkalosis causes bicarbonaturia, which results in urinary sodium loss and a urine sodium concentration of >20 mEq/L. In this setting, a low urinary chloride (i.e., <10 mEq/L) can be a surrogate marker of sodium avidity.

The absence of markers of sodium avidity (i.e., a urine sodium >20 mEq/L without vomiting) suggests that hypovolemia is the result of urinary fluid loss instead. This situation is most commonly seen with diuretic use, which warrants further discussion given its frequency as a cause of hyponatremia in both inpatient and outpatient settings [29, 30]. The risk for diuretic-induced hyponatremia appears to increase with advancing age and decreasing body mass, and this phenomenon appears to be more common in women [31, 32]. The elderly may be at particular risk due to an age-related decrease in the ability to excrete a water load, a defect that is magnified in the presence of thiazide diuretics [33]. Hyponatremia typically occurs within the first 2 weeks of therapy [34].

Thiazides are virtually always the culprit in diuretic-induced hyponatremia. Unlike loop diuretics, thiazides interfere with solute reabsorption in the diluting segment of the nephron, preventing the kidney from generating a maximally dilute urine. In addition, diuretics can induce volume depletion, causing decreased distal fluid delivery and increased AVP release, and both of these consequences can contribute to hyponatremia in the setting of already impaired urinary dilution. Loop diuretics, in contrast, block solute reabsorption in the ascending limb of the loop of Henle, thereby diminishing the establishment of a hypertonic gradient throughout the medulla. As a result, even if a loop diuretic induces enough volume depletion to stimulate AVP release, the diminution of medullary hypertonicity limits the urinary concentration that AVP would otherwise mediate in the collecting duct, thereby counteracting free water retention and preventing hyponatremia [35].

Potassium depletion can also contribute to hyponatremia in the setting of diuretic use and intravascular volume depletion. Hypokalemia can induce an efflux of potassium from the intracellular compartment in order to replete the diminished extracellular store. To maintain electroneutrality, this potassium efflux is matched by extracellular sodium movement into the intracellular compartment. Sodium loss from the ECF can produce a drop in serum sodium concentration in the setting of volume depletion, when secondarily elevated AVP levels prevent the compensatory water diuresis that would otherwise normalize the serum sodium concentration.

The impact of hypokalemia on this type of hyponatremia is suggested by studies that show exogenous potassium chloride can improve the hyponatremia even in the absence of sodium repletion [36–38].

Other less common causes of renal solute losses that can cause hyponatremia through AVP stimulation include mineralocorticoid deficiency or resistance [39], adrenal insufficiency [40], osmotic diuresis, and salt-wasting nephropathy. This latter condition can arise in the setting of polycystic kidney disease [41] or interstitial nephritis [42].

Euvolemic Hyponatremia

Euvolemic hyponatremia results from an increase in total body water without a change in total body sodium. This form of hyponatremia is the most commonly encountered among hospitalized patients [14] and has a variety of potential causes that share a common underlying physiology—AVP release that is unregulated and unprovoked by either osmotic or non-osmotic stimuli. In this regard, the most well-recognized cause of euvolemic hyponatremia is the syndrome of inappropriate antidiuretic hormone (SIADH), which is the most common overall etiology of hyponatremia [43].

Syndrome of Inappropriate Antidiuretic Hormone

SIADH classically results from elevated AVP levels during conditions in which pituitary AVP release should be suppressed. A variety of etiologies may underlie this inappropriate AVP release, but regardless of the inciting cause, the elevated AVP levels result in urine that is inappropriately concentrated with respect to plasma tonicity, and this relative water retention dilutes the serum sodium concentration. These patients do not develop edema for two reasons. First, because two-thirds of total body water is retained in cells, water retention tends not to cause the ECF volume expansion that results in edema. Second, any significant water retention in the intravascular space will activate volume receptors that trigger a compensatory natriuresis that offsets any volume expansion. Of note, the resulting negative sodium balance can contribute somewhat to the hyponatremia [see (2.5)]. In the setting of persistently elevated plasma AVP levels, an escape from AVP-induced water retention may occur over time due to downregulation of AQP2 channels [44], but hyponatremia will still occur in this setting unless water intake is restricted.

SIADH is diagnosed by exclusion. Its diagnostic characteristics include hypotonic hyponatremia in the setting of clinical euvolemia and an inappropriately elevated urinary osmolarity. These findings in a patient who is not taking diuretics or other drugs associated with hyponatremia should elicit a work up for other causes of euvolemic hyponatremia, with a strong suspicion for SIADH. A negative evaluation for these other conditions such as hypothyroidism and adrenal insufficiency allows an exclusionary diagnosis of SIADH to be made [45].

Once the diagnosis is made, an attempt to find the underlying cause of SIADH should be endeavored. Idiopathic SIADH is a relatively rare phenomenon but appears to be more common in elderly patients [46–48]. The observation that both hyponatremia in general and idiopathic SIADH in specific are more common among the elderly [49, 50] suggests that AVP regulation changes as people age. To that point, a higher sensitivity to osmotic stimuli has been demonstrated in older subjects [51]. Not surprisingly, therefore, there is evidence that hyponatremia is more common in older patients in general and as a hospital-acquired phenomenon as well [52]. Still, when overt SIADH is observed in any patient in the absence of obvious causes, an extensive and age-appropriate work up for occult malignancy should be made before the SIADH is labeled idiopathic, as hyponatremia is occasionally the presenting abnormality with certain cancers.

While true idiopathic SIADH is rare, secondary causes are more common. As alluded to above, malignancies are one of the most common causes of SIADH. Bronchogenic carcinoma of the lung, especially small-cell lung cancer, is one of the most frequent associations, with incidences reported up to 11 % overall [53] and 33 % in patients with more extensive disease [54]. Head and neck cancers are also commonly associated with SIADH [55], and cancers of the pancreas or duodenum are other reported associations. The mechanism of malignancy-related SIADH is often related to ectopic AVP production within the malignant tissue.

Central nervous system disorders such as hemorrhage, tumor, and infection are also frequent underlying processes for SIADH. These varied disorders can cause SIADH by stimulating excess AVP release from the pituitary, either by diminishing the tonic inhibition of AVP release or enhancing AVP-stimulatory pathways. Respiratory failure from a variety of pulmonary disorders (including acute pneumonia [56–58], chronic obstructive lung disease [59], and tuberculosis [60]) has been particularly associated with SIADH.

In addition to these broad categories of SIADH causes, the disorder has also been increasingly recognized as a complication in hospitalized patients with the acquired immunodeficiency syndrome (AIDS). Hyponatremia is seen in up to 38 % of AIDS patients, and SIADH has been reported as the etiology in up to 68 % of those cases [61]. Stress, pain, and postoperative status are also potential underlying causes of SIADH.

Irrespective of the cause of SIADH, four different patterns of AVP release have been described in SIADH [62]. In the so-called Type A pattern, AVP release occurs erratically and independently of plasma osmolarity, and the dissociation between AVP levels and plasma osmolarity results in osmotic dysregulation and consequent hyponatremia. Type B, or "reset osmostat," bears similarity to normal AVP release patterns, in which a linear relationship exists between AVP and plasma osmolarity. However, as compared to individuals with normal AVP release, patients with this type of SIADH have higher AVP levels for any given plasma osmolarity. Like normal individuals, these patients have osmoreceptors that respond to changes in plasma tonicity, but their set point for AVP release is lower than normal. These patients suppress AVP in response to a water load and increase AVP in response to increased plasma tonicity, resulting in stable hyponatremia around the new

set point. Reset osmostat most commonly occurs during pregnancy [63–65] and can also be seen in patients with chronic malnutrition [66]. In addition, reset osmostat may contribute to the multifactorial hyponatremia seen in patients with psychosis [19, 26] Urine in patients with reset osmostat can be dilute or non-dilute depending on their individual set point and their plasma tonicity. The Type C pattern of SIADH involves appropriate AVP release in the setting of normal or elevated plasma osmolarity, but an inability to suppress AVP secretion beyond a certain level during water loading. The least common pattern, called Type D, involves an apparently normal relationship between AVP secretion and plasma osmolarity but an increased sensitivity to the effects of AVP. Some of these type D patients may have gain-of-function mutations in the V2 receptor that result in so-called nephrogenic syndrome of inappropriate antidiuresis [67, 68].

Finally, medication-related hyponatremia is a particularly prominent cause of euvolemic hyponatremia, and the mechanism in many cases is stimulation of AVP release or potentiation of the renal action of AVP. In the former category, selective serotonin reuptake inhibitors are the most prominent, as well as carbamazepine, vincristine, and narcotics. The latter mechanism has been observed with chlorpropramide, cyclophosphamide, and nonsteroidal anti-inflammatory drugs.

Hyponatremia in Endocrinopathies

In addition to SIADH, a variety of less common causes of euvolemic hyponatremia also exist. Of note, hyponatremia is often seen in patients with primary adrenal insufficiency particularly when in the midst of an Addisonian crisis. Animal models involving AVP gene mutations and/or surgical adrenalectomies have helped elucidate the roles played by both mineralocorticoid deficiency and glucocorticoid deficiency in sodium and water homeostasis.

The mineralocorticoid deficiency seen in some cases of adrenal insufficiency can produce enough renal sodium wasting to cause hypovolemia and consequent non-osmotic AVP release, resulting in a hypovolemic type of hyponatremia. This mechanism has been proven by studies in which the low serum sodium levels of mineralocorticoid-deficient animals can be corrected simply by reversing their negative sodium balance [69]. However, it has been shown that animals with hypopituitarism can develop hyponatremia as well, despite the fact that this condition does not involve mineralocorticoid deficiency. This observation points to a separate role of glucocorticoid deficiency in the hyponatremia of adrenal insufficiency, and the pathogenesis of this hyponatremia is multifactorial.

There is evidence that glucocorticoids have a direct inhibitory effect on AVP expression in magnocellular neurons and are therefore required for complete suppression of AVP. As such, glucocorticoid deficiency removes the normal, tonic inhibition of AVP release and therefore results in inappropriately non-suppressed AVP levels in settings of normal plasma tonicity, leading to hyponatremia [70]. Second, AVP release can be further stimulated by the baroreceptor pathway that detects the decreased cardiac output and blood pressure that can accompany

glucocorticoid deficiency [71]. Third, in addition to these AVP-related mechanisms, AVP-independent factors exist, as a diluting defect is seen in genetically AVP-deficient, surgically adrenalectomized animals [72] and is fully corrected by steroid replacement [73]. A possible explanation for this observation is that glucocorticoid deficiency has been associated with increased collecting duct AQP2 expression [74], suggesting that glucocorticoids are required to render the collecting duct water impermeable. Taken together, glucocorticoid deficiency can result in hyponatremia with an elevated urine sodium concentration that is difficult to distinguish from SIADH but that will improve with glucocorticoid replacement alone.

Euvolemic hyponatremia may also complicate hypothyroidism, particularly in cases of severe primary hypothyroidism with myxedema [75, 76]. The proposed mechanism of this hyponatremia is related at least in part to non-osmotic AVP release due to poor cardiac output, as well as increased AQP2 expression in the collecting duct [77]. This hypothesis is supported by animal models of severe hypothyroidism as well as the observation that hypothyroid patients may fail to suppress AVP fully when water-loaded [78]. However, other factors are likely involved as decreased perfusion alone would likely cause significant sodium avidity, and the urine sodium concentration in this condition is not necessarily low [79]. As such, it is speculated that alterations of renal hemodynamics are also involved in the pathogenesis of this hyponatremia, and studies in surgically hypothyroid animals with congenital AVP-deficiency have suggested AVP-independent effects related to systemic and renal hemodynamics [80]. Thyroid hormone replacement has been shown to improve water excretion both in experimental models and in patients with this condition [77].

Exercise-Associated Hyponatremia

Exercise-associated hyponatremia has been the subject of some recent interest. This type of hyponatremia, an occasional complication of extreme exercise events like marathons and ultramarathons, can be associated with significant morbidity and mortality. The pathogenesis is felt to be multifactorial. First, significantly increased water intake is an essential component to the development of hyponatremia [81]. Positive water balance results from the concurrence of this increased water intake and submaximal urinary dilution, which results from the non-osmotic AVP release stimulated by the exercise itself [82] and the nausea [83], pain [84], and hypoglycemia [85] that can accompany it. This so-called inappropriate AVP release can be augmented by "appropriate" AVP release if hypovolemia has occurred due to sodium losses in sweat. Taken together, the concurrent excess water intake and impaired urinary dilution result in positive water balance and hyponatremia, occasionally with fatal consequences. Accordingly, investigators have identified the following features associated with hyponatremia in marathon runners: consumption of over 3 L during the marathon, ingestion of fluids at every mile of the race, racing time over 4 h, female gender, and low body mass index [86].

Hypervolemic Hyponatremia

Finally, hypervolemic hyponatremia occurs when there is an increase in both total body sodium and water, with the retention of water occurring out of proportion to the sodium retention. This disorder is primarily seen with the edematous states (especially congestive heart failure and cirrhosis), and the degree of hyponatremia can serve as a marker for the severity of the underlying disorder as well as a prognostic indicator. The pathogenesis of hyponatremia in these conditions is related to the hormonal and intrarenal consequences of low EABV [87].

Advancing congestive heart failure (CHF) is often associated with hyponatremia [71, 88] and is a marker for poor prognosis [89]. Cardiopulmonary congestion and low left-sided cardiac output result in arterial underfilling, which is sensed by mechanoreceptors in the left ventricle, carotid sinus, aortic arch, and renal afferent arterioles [90]. Activation of these mechanoreceptors produces increased sympathetic outflow and activation of the renin–angiotensin–aldosterone system, and these pathways lead to decreases in GFR and increases in proximal tubular reabsorption. The consequences of these changes are decreased water delivery to the distal nephron and interference with the establishment of a medullary interstitial tonicity gradient, therefore impairing free water clearance. Activation of those mechanoreceptors also leads to non-osmotic stimulation of AVP release and increased thirst, which produce hyponatremia as AVP interferes with urinary dilution while increased thirst sensation causes increased water intake. Additionally, AQP2 expression has been shown to be increased in animal models of advanced CHF [91], allowing for even greater water reabsorption in the presence of AVP. The frequent use of diuretics in this setting can further lower the EABV and thereby contribute to the hyponatremia.

Cirrhosis is another common setting in which hypervolemic hyponatremia can be seen [71]. Vasodilation in both the splanchnic and peripheral circulation result in low EABV. As in CHF, this fall in EABV is detected by mechanoreceptors and leads to a similar cascade of neurohumoral pathway activation that culminates in non-osmotic AVP release, increased thirst, and decreased distal delivery of fluid, all of which produce hyponatremia. High AVP levels have been demonstrated in cirrhotic humans [92], and animal models have demonstrated upregulated AQP2 in cirrhosis as well [93]. AVP-independent mechanisms have also been proposed in cirrhosis-related hyponatremia. As in CHF, the concomitant use of diuretics can exacerbate the situation by further reducing EABV.

Hypervolemic hyponatremia has been reported in the nephrotic syndrome as well, but the presence of hyponatremia in this condition is inconsistent and appears to be unrelated to disease severity. Some investigators feel that patients with severe urinary protein loss may lose enough oncotic pressure that they have diminished EABV, leading to hyponatremia through the neurohormonal mechanisms described above. However, there is disagreement on whether this physiology truly occurs in all patients with the nephrotic syndrome, particularly those with lower glomerular filtration rate in which the vasculature may be expanded.

Patients with renal failure (either acute or chronic) also can develop hypervolemic hyponatremia; [14, 94] a recent report showed a 15 % prevalence of hyponatremia in patients with CKD [95]. In renal failure, the increased solute clearance burden placed on each remaining nephron creates an osmotic diuresis that causes the minimal urine osmolarity to rise from 50 mOsm/L to as high as 250 mOsmol/L despite suppression of AVP [96]. This dilutional impairment allows these patients to drink in excess of their maximal free water clearance capability more easily. It is important to note that patients with advanced renal failure often have high measured plasma osmolarity because of high blood urea nitrogen levels. However, their hyponatremia can still be considered hypotonic in nature because urea is an ineffective osmole due to its free membrane permeability, and therefore, hyponatremia in these patients is associated with a low effective plasma osmolarity.

As mentioned above, in addition to the non-osmotic stimulation of AVP release causing hyponatremia in these edematous disorders, hyponatremia can also be related to the diminished distal delivery of fluid that results from decreased GFR and increased proximal tubular reabsorption. While the diminished EABV at the root of this physiology should also result in renal sodium avidity due to secondary hyperaldosteronism, the measured urine sodium will not necessarily be low, as concurrent diuretic use is common, and urine sodium conservation can be interrupted by acute kidney injury and proximal tubular dysfunction in this setting.

Conclusion

The physiology of water balance involves a complex system of transport processes in the kidney and the tight hormonal control of water excretion that acts in concert with those mechanisms. Maintenance of strict water balance is essential in keeping the serum sodium concentration stable, and this regulation in turn produces a stable plasma osmolarity. The importance of this stability is evident when water balance mechanisms are disrupted, and the pathophysiology of hyponatremia can be understood with respect to these water balance considerations. Using these concepts, a systematic approach to laboratory results showing low serum sodium concentrations will allow for an understanding of the underlying processes and will assist in formulating a treatment approach for this widespread clinical problem.

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Chapter 3
Utility of Electrolyte-Free Water Clearance in the Analysis and Treatment of the Dysnatremias

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Hyponatremia is the most common electrolyte disorder in hospitalized patients [1]. Hyponatremia is a clinical disorder often attributed to impaired urinary free water excretion resulting from persistent release of antidiuretic hormone (ADH). As hyponatremia is often characterized by a defect in urinary free water excretion, an analysis of free water clearance (FWC) and electrolyte-free water clearance (EFWC) is a helpful clinical tool that can be utilized to characterize the rate of urinary free water excretion in this disorder [2–4]. In this chapter, we will discuss the concepts of FWC and EFWC, their limitations, and their utility in the evaluation and management of the dysnatremias (Table 3.1).

Free Water Clearance

The concept of free water clearance (FWC) was introduced in 1952 as a comparison of urine to plasma osmolality to determine whether the kidney is excreting dilute urine and to quantify the rate of urinary free water excretion [2]. To determine

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Table 3.1 Free water clearance formulas

FWC	EFWC	MEFWC[a]	WB-EFWC[b]
$V(1 - U_{osm}/P_{osm})$	$V\left(1 - \frac{[Na^+ + K^+]_{urine}}{[Na^+]_p}\right)$	$V\left(1 - \frac{1.03[Na^+ + K^+]_{urine}}{[Na^+]_p + 23.8}\right)$	$V_{MB} - \frac{1.03E_{MB}}{[Na^+]_p + 23.8}$

[a]In the setting of hyperglycemia, the generalized MEFWC formula is utilized where
$\text{MEFWC} = V\left(1 - 1.03[Na^+ + K^+]_{urine}/\left([Na^+]_p + 23.8 + (1.6/100)\left([glucose]_p - 120\right)\right)\right)$
[b]In the setting of hyperglycemia, the WB-EFWC formula must be generalized as follows:
$\text{WB–EFWC} = V_{MB} - 1.03E_{MB}/\left([Na^+]_p + 23.8 + (1.6/100)\left([glucose]_p - 120\right)\right)$

FWC, total urinary volume is viewed as having two components: a component containing urinary solutes in a solution that is isosmotic to plasma (osmolal clearance), and a second component that consists of solute-free water (free water clearance):

$$\text{Total urine volume } (V) = \text{Osmolal clearance} + \text{Free water clearance } (cH_2O)$$
$$V = V(U_{osm}/P_{osm}) + cH_2O$$
$$cH_2O = V(1 - U_{osm}/P_{osm}) \quad (3.1)$$

There is an important limitation inherent in the calculation of free water clearance (cH_2O, or FWC). As urea is a component of the measured plasma and urine osmolality, FWC is thought to be less accurate than EFWC in predicting changes in the plasma $[Na^+]$ ($[Na^+]_p$) because urea is an "ineffective" osmole [3]. However, this is a common misconception. As urea has a high permeability across cell membranes, urea is indeed an "ineffective" osmole in the plasma since it does not alter the distribution of water between the body fluid compartments. However, urea does have a modulating effect on the plasma $[Na^+]$ since it is an osmotically active solute in the urine. Indeed, it is well known that urea induces an osmotic diuresis, thereby resulting in the urinary excretion of H_2O in excess of Na^+ and K^+ [5]. Moreover, urea has also been utilized to increase the daily urinary solute excretion and therefore urinary EFWC in patients with the syndrome of inappropriate antidiuretic hormone secretion (SIADH) [6]. Rather, the major limitation of FWC is due to the fact that urine that is isomotic to the plasma osmolality is not necessarily isonatric to the plasma $[Na^+]$.

Electrolyte-Free Water Clearance

Electrolyte-free water clearance (EFWC) is superior to FWC since it is based on isonatric electrolyte clearance rather than isosmolar solute clearance. In the case of EFWC, urine is viewed conceptually as having two components: one component containing a concentration of $Na^+ + K^+$ that is isonatric to the plasma $[Na^+]$

(isonatric electrolyte clearance), and a second component which does not contain Na^+ and K^+ salts and is termed electrolyte-free water (electrolyte-free water clearance). The isonatric urinary component by definition will not change the plasma $[Na^+]$ ($[Na^+]_p$) if excreted or absorbed, whereas the electrolyte-free water component will change the $[Na^+]_p$ if excreted or absorbed:

$$\begin{aligned}\text{Total urine volume } (V) = {} & \text{Isonatric electrolyte clearance} \\ & + \text{Electrolyte-free water clearance } (cH_2O_e)\end{aligned}$$

$$\begin{aligned} V &= V[Na^+ + K^+]_{urine}/[Na^+]_p + cH_2O_e \\ cH_2O_e &= V\left(1 - [Na^+ + K^+]_{urine}\ /[Na^+]_p\right) \end{aligned} \tag{3.2}$$

However, the EFWC formula is not without its limitations. The major limitation of the EFWC formula previously derived by Goldberg is that it is based on the assumption that $[Na^+]_p = (Na_e + K_e)/TBW$ [3]. This formula fails to consider the empirical relationship between the plasma water $[Na^+]$ ($[Na^+]_{pw}$), total exchangeable Na^+ (Na_e), total exchangeable K^+ (K_e), and TBW originally demonstrated by Edelman et al.: $[Na^+]_{pw} = 1.11(Na_e + K_e)/TBW - 25.6$ [7]. Specifically, it fails to consider the quantitative and physiological significance of the slope and intercept in the Edelman equation in its derivation.

Physiologic Determinants of the Plasma Water Sodium Concentration as Reflected in the Edelman Equation

In deriving the EFWC formula, the complete Edelman equation,

$$[Na^+]_{pw} = 1.11(Na_e + K_e)/TBW - 25.6 \tag{3.3}$$

should be used as the slope and intercept of this equation have been shown to have quantitative and physiologic significance [8]. There are several physiologically relevant parameters determining the magnitude of the slope and intercept which independently alter the $[Na^+]_{pw}$ [8]:

$$\begin{aligned}[\mathbf{Na}^+]_{\mathbf{pw}} = {} & G/\varnothing\,\frac{(Na_e + K_e)}{\mathbf{TBW}} \\ & - G/\varnothing\left[\frac{(Na_{osm\ inactive} + K_{osm\ inactive})}{TBW} - \frac{(osmol_{ICF} + osmol_{ECF})}{TBW} + [K^+]_{pw} + \frac{osmol_{pw}}{V_{pw}}\right]\end{aligned} \tag{3.4}$$

where $G = \left(Vol_{pw}\ + Vol_{ISF}\right)/\left(Vol_{pw} + R\ x\ Vol_{ISF}\right)$

$\varnothing$ = average osmotic coefficient of Na^+ salts; R = Gibbs–Donnan ratio for the distribution of univalent cations between the plasma and interstitial fluid; Vol_{pw} = plasma water volume; Vol_{ISF} = interstitial fluid volume; $Na_{osm\ inactive}$ = osmotically inactive Na^+; $K_{osm\ inactive}$ = osmotically inactive K^+; $osmol_{ECF}$ = osmotically active, extracellular non-Na^+ and non-K^+ osmoles; $osmol_{ICF}$ = osmotically active, intracellular non-Na^+ and non-K^+ osmoles; $[Na^+]_{pw}$ = plasma water Na^+ concentration; $[K^+]_{pw}$ = plasma water K^+ concentration; $osmol_{pw}$ = osmotically active, plasma water non-Na^+ non-K^+ osmoles.

Equation 3.4 defines all the physiologic factors that determine the magnitude of the $[Na^+]_{pw}$. Simplistically, $[Na^+]_{pw}$ is a function of the quantity of Na^+ ions and volume of water in the plasma space:

$$[Na^+]_{pw} = \text{quantity of plasma } Na^+ / \text{volume of plasma water} \tag{3.5}$$

Therefore, any physiologic factor which alters the numerator and/or denominator of this ratio will modulate the $[Na^+]_{pw}$ and is a determinant of the $[Na^+]_{pw}$. Recently, the slope and intercept of the Edelman equation have been shown to represent physiologic factors that modulate both the numerator and denominator of the ratio in Eq. 3.5.

The slope of the Edelman equation is represented by the term $G/\varnothing$ in Eq. 3.4. The term G in the slope is a reflection of the effect of Gibbs–Donnan equilibrium on the $[Na^+]_{pw}$ [8]. Due to the presence of negatively charged, impermeant proteins in the plasma space, the distribution of Na^+ is altered in order to preserve electroneutrality in the plasma and interstitial fluid compartments, thereby resulting in a greater $[Na^+]_{pw}$ as compared to the interstitial fluid sodium concentration ($[Na^+]_{ISF}$) [9]. Therefore, Gibbs–Donnan equilibrium modulates the $[Na^+]_{pw}$ by altering the numerator of the ratio in Eq. 3.5. Additionally, the osmotic coefficient $\varnothing$ in the slope accounts for the effectiveness of Na^+ salts as independent osmotically active particles under physiological conditions since the osmotic activity of most ionic particles is slightly less than one due to the electrical interactions between the ions [10]. Consequently, the osmotic activity of Na^+ salts will determine the distribution of water within the plasma space and therefore modulate the denominator of the ratio in Eq. 3.5.

There are also several physiologically relevant parameters in Eq. 3.4 that determine the magnitude of the intercept in the Edelman equation and that independently modulate the $[Na^+]_{pw}$: (1) osmotically inactive Na_e and K_e; (2) plasma water $[K^+]$; (3) intracellular and extracellular osmotically active non-Na^+ and non-K^+ osmoles; and (4) plasma osmotically active non-Na^+ and non-K^+ osmoles [8]. In essence, the physiologic factors contributing to the magnitude of the intercept in the Edelman equation represent the role of non-Na^+ osmotically active solutes in modulating the $[Na^+]_{pw}$. Since the body fluid compartments are in osmotic equilibrium with each other, all non-Na^+ osmotically active solutes determine the distribution of water in the plasma space and modulate the denominator of the ratio in Eq. 3.5. Thus, all non-Na^+ osmotically active solutes must also be determinants of the $[Na^+]_{pw}$.

It is also well appreciated that not all Na_e and K_e are osmotically active as a portion of Na_e is bound in bone and a portion of cellular K^+ is reduced in its mobility and in its osmotic activity due to its association with anionic groups such as carboxyl groups on proteins or to phosphate groups in creatine phosphate, adenosine triphosphate (ATP), proteins, and nucleic acids [11–13]. Since osmotically inactive Na_e and K_e do not contribute to the distribution of water between the plasma and non-plasma compartments, osmotically inactive Na_e and K_e cannot contribute to the modulation of the $[Na^+]_{pw}$ and is reflected by the intercept of the Edelman equation.

Modified Electrolyte-Free Water Clearance

Taking into account the aforementioned factors which also modulate the plasma $[Na^+]$, Nguyen derived a new formula termed MEFWC (modified electrolyte-free water clearance) for determining the electrolyte-free water clearance taking into consideration the empirical relationship between the $[Na^+]_{pw}$ and Na_e, K_e, and TBW [4]. Because the previous EFWC formula does not consider the quantitative and physiological significance of the slope and intercept in the Edelman equation, it implicitly assumes in its derivation that urine is isonatric to the $[Na^+]_p$ when $[Na^+ + K^+]_{urine}$ is equal to the $[Na^+]_p$. MEFWC, unlike the previous EFWC formula, is derived based on the requirement of the Edelman equation that urine is isonatric (i.e., urinary electrolyte-free water clearance is zero) only when $[Na^+ + K^+]_{urine} = (Na_e + K_e)/TBW = 0.97[Na^+]_p + 23.1$ [4]:

$$\text{MEFWC} = V\left(1 - 1.03[Na^+ + K^+]_{urine}/\left([Na^+]_p + 23.8\right)\right) \tag{3.6}$$

Furthermore, MEFWC incorporates in its derivation the fact that plasma is 93% water [14, 15]. The MEFWC formula can also be expanded to account for the clinical scenario in which hyperglycemia may be a contributing factor to the hyponatremia [4]:

$$\text{MEFWC} = V\left(1 - 1.03[Na^+ + K^+]_{urine}/\left([Na^+]_p + 23.8 + (1.6/100)\left([\text{glucose}]_p - 120\right)\right)\right) \tag{3.7}$$

Equation 3.7 accounts for the fact that hyperglycemia-induced hyponatremia results from changes in the mass balance of Na^+, K^+, and H_2O (glucose-induced osmotic diuresis) as well as from the dilutional effect of hyperglycemia induced by the translocation of water from the intracellular fluid compartment to the extracellular fluid compartment [4]. However, as with previous FWC and EFWC formulas, MEFWC cannot quantitatively predict the directional change in the $[Na^+]_p$ since it does not account for the input and non-renal output of Na^+, K^+, and H_2O.

Whole Body Electrolyte-Free Water Clearance

FWC, EFWC, and MEFWC are regarded as the classic equations used for quantifying the urinary free water excretion in the analysis of the dysnatremias. However, an important limitation of these formulas is that they do not account for the input of Na^+, K^+, and H_2O. Neither do they account for the non-renal output of Na^+, K^+, and H_2O. By analyzing only the urinary component, this inherently makes it difficult to accurately predict the directional change in the plasma $[Na^+]$.

It is therefore invaluable for both the input and output of Na^+, K^+, and H_2O to be included in the analysis of the dysnatremias. In accounting for the mass balance of Na^+, K^+, and H_2O in the pathogenesis of the dysnatremias, Nguyen derived a new formula termed whole body electrolyte-free water clearance (WB-EFWC) [16]:

$$\text{WB}-\text{EFWC} = V_{\text{MB}} - \frac{1.03\text{E}_{\text{MB}}}{[\text{Na}^+]_{\text{p}} + 23.8} \tag{3.8}$$

where $[E] = [Na^+ + K^+]$, V = volume,

$$E_{\text{MB}} = \text{mass balance of } \text{Na}^+ + \text{K}^+ = [E]_{\text{input}} \times V_{\text{input}} - [E]_{\text{output}} \times V_{\text{output}},$$

$$V_{\text{MB}} = \text{mass balance of water} = V_{\text{input}} - V_{\text{output}}.$$

Thus, WB-EFWC can predict the directional change in the $[Na^+]_p$ by accounting for the relative effects of E_{MB} (mass balance of $Na^+ + K^+$) and V_{MB} (mass balance of H_2O) on the $[Na^+]_p$. The value of WB-EFWC can be either positive or negative. If the input and output of Na^+, K^+, and H_2O result in a net loss of electrolyte-free water, WB-EFWC will be negative in value and the $[Na^+]_p$ will increase; whereas WB-EFWC will be positive in value and the $[Na^+]_p$ will be lowered if the mass balance of Na^+, K^+, and H_2O results in the retention of electrolyte-free water.

In the setting of hyperglycemia, the WB-EFWC formula must be generalized as follows:

$$\text{WB}-\text{EFWC} = V_{\text{MB}} - \frac{1.03E_{\text{MB}}}{[\text{Na}^+]_{\text{p}} + 23.8 + (1.6/100)([\text{glucose}]_{\text{p}} - 120)} \tag{3.9}$$

Equation 3.9 accounts for the effect of changes in the mass balance of Na^+, K^+, and H_2O as well as the dilutional effect of hyperglycemia attributable to the osmotic shift of water on the $[Na^+]_p$ [16].

Utility of Electrolyte-Free Water Clearance in the Analysis of the Dysnatremias

The pathogenesis of hyponatremia is largely characterized by disorders of urinary dilution. The normal physiology of urinary dilution is determined by numerous factors such as normal glomerular filtration rate, adequate delivery of H_2O to the diluting segments of the nephron mediated by inhibition of proximal Na^+ and H_2O absorption, intact Na^+ and Cl^- reabsorption at both the thick ascending limb of the loop of Henle and distal convoluted tubules, and the inhibition of H_2O absorption at the collecting duct resulting from the suppression of antidiuretic hormone (ADH) secretion. In the setting of ongoing free water intake, any disruption in the mechanisms involved with dilute urine formation can lead to hyponatremia. Determination of MEFWC is therefore useful in defining the renal diluting defect by characterizing the rate of urinary electrolyte-free water excretion.

Importantly, MEFWC can also be utilized to analyze the generation of the dysnatremias. The dysnatremias result from an imbalance in the input and output of Na^+, K^+, and H_2O. Consequently, changes in the plasma $[Na^+]$ can be predicted based on the relation between electrolyte-free water intake and urinary MEFWC. Assuming that insensible water loss and fecal water loss approximate the water content of ingested food and water of oxidation [17], hyponatremia will ensue in clinical settings where electrolyte-free water intake is greater than urinary MEFWC. Accordingly, hypernatremia will result when electrolyte-free water intake is less than urinary MEFWC. Therefore, MEFWC is a useful tool in defining the pathogenesis of the dysnatremias. Similarly, WB-EFWC is an important clinical tool in defining the generation of hyponatremia and hypernatremia by accounting for the effect of changes in the mass balance of Na^+, K^+, and H_2O on the $[Na^+]_p$ as discussed earlier [16]. WB-EFWC is particularly helpful in defining the pathogenesis of the dysnatremias in clinical settings in which there are various sources of input and output of Na^+, K^+, and H_2O.

Utility of Electrolyte-Free Water Clearance in the Treatment of Hyponatremia

MEFWC as a Tool to Determine the Degree and Efficacy of Free Water Restriction

There are several strategies for the correction of hyponatremia. As the plasma $[Na^+]$ is determined by the total exchangeable Na^+ and K^+ in relation to total body water, the basic therapeutic approach to hyponatremia is based on either increasing the total exchangeable Na^+ and K^+ or decreasing the amount of total body water.

In hypovolemic hyponatremia, the goal is to replete the Na^+, K^+ and H_2O deficit; whereas in dilutional hyponatremia, the goal is to induce negative free water balance.

In euvolemic and hypervolemic hyponatremia, the goal is therefore to limit electrolyte-free water intake to less than urinary electrolyte-free water excretion assuming that insensible water loss and fecal water loss approximate the water content of ingested food and water of oxidation [17]. Toward this goal, MEFWC is a useful clinical tool that helps to determine the degree of free water restriction required to correct the plasma [Na^+]. Specifically, electrolyte-free water intake must be restricted to less than the urinary MEFWC in order to induce negative free water balance. However, adherence to strict free water restriction is difficult in terms of compliance in cases where the urinary MEFWC is very low. Moreover, free water restriction is not effective in correcting the plasma [Na^+] in cases where the urinary MEFWC is negative in value. In this clinical setting, there is increased urinary electrolyte-free water reabsorption (rather than urinary electrolyte-free water excretion) resulting from the elevated ADH secretion, and any amount of electrolyte-free water intake will tend to lower the plasma [Na^+]. In such cases, dilutional hyponatremia can only be corrected by increasing urinary electrolyte-free water excretion in excess of electrolyte-free water intake. Therefore, urinary MEFWC is a useful clinical tool in determining the effectiveness and feasibility of free water restriction. Specifically, the amount of free water restriction needed to achieve negative free water balance is calculated via the MEFWC formula.

Clinical Example

Patient is a 55-y.o. male who presented with hyponatremia secondary to the syndrome of inappropriate antidiuretic hormone secretion (SIADH). On initial presentation, plasma [Na^+] was 120 mmol/L, urinary [$Na^+ + K^+$] was 100 mmol/L, and urinary volume was 1.5 L/day. As the urinary volume was 1.5 L/day, the patient was placed on 1 L free water restriction. However, this degree of free water restriction resulted in a decrement in the plasma [Na^+]. Why was free water restriction ineffective in this patient?

$$\text{MEFWC} = V\left(1 - 1.03[\text{Na}^+ + \text{K}^+]_{\text{urine}}/\left([\text{Na}^+]_{\text{p}} + 23.8\right)\right)$$

$$\text{MEFWC} = 1.5(1 - 1.03(100)/(120 + 23.8)) = 0.43 \text{ L}$$

Assuming that insensible water loss and fecal water loss approximate the water content of ingested food and water of oxidation [17], electrolyte-free water intake must be restricted to less than urinary electrolyte-free water excretion as determined by MEFWC in order to achieve negative free water balance. In this particular case, the patient's electrolyte-free water intake was in excess of the urinary electrolyte-free water clearance, thereby resulting in a decrement in the plasma [Na^+].

Therefore, the patient's electrolyte-free water intake must be restricted to less than 0.43 L in order to raise the plasma [Na^+]. Such strict free water restriction would be difficult to adhere to and is not feasible as a therapeutic option. Hence, alternative approaches should be undertaken to achieve negative free water balance in this case.

Alternative Approaches in Achieving Negative Free H_2O Balance

There are several alternative approaches in achieving negative free water balance in the treatment of dilutional hyponatremia in cases where a restricted free water intake is not feasible. In these cases, negative free water balance is achieved by increasing urinary MEFWC rather than decreasing electrolyte-free water intake. Currently, there are two common approaches to increasing the urinary MEFWC: an increase in dietary solute intake and the utility of vasopressin 2 receptor antagonist.

An increase in dietary solute intake plays an important role in increasing urinary electrolyte-free water clearance [18]. As previously discussed, $cH_2O_e = V - IEC$ (isonatric electrolyte clearance); therefore, any intervention that is able to increase urinary volume will also increase urinary electrolyte-free water clearance. An increase in dietary solute intake will lead to an equivalent increase in daily urinary solute excretion in the steady state. As reflected by the following equation, urinary solute excretion = urinary volume (V) × urine osmolality (U_{osm}), urinary volume is directly proportional to daily solute excretion. Thus, V = solute excretion/U_{osm}. Consequently, at any given urinary osmolality, as daily solute excretion increases so does total urinary volume, thereby leading to an increase in urinary electrolyte-free water clearance, cH_2O_e. Increased daily solute intake is particularly useful in patients with the syndrome of inappropriate antidiuretic hormone secretion (SIADH) given the fixed defect in urinary free water excretion, i.e., relatively fixed urinary osmolality [6]. In these cases, increasing dietary solute intake with either salt tablets or an increased protein intake will result in increased urinary volume and eventually increased urinary electrolyte-free water clearance.

Clinical Example

Patient is a 60-y.o. male who presented with hyponatremia secondary to SIADH. On initial presentation, plasma [Na^+] was 125 mmol/L, urinary osmolality was 300 mOsm/kg, urinary Na^+ excretion was 80 mmol/day, urinary K^+ excretion was 20 mmol/day, and daily solute excretion was 600 mOsm/day.

$$\text{Urinary volume} = \text{solute excretion}/U_{osm} = 600/300 = 2\ \text{L/day}$$

Therefore,

$$\text{Urine } [\text{Na}^+] = 80/2 = 40 \text{ mmol/L}$$

$$\text{Urine } [\text{K}^+] = 20/2 = 10 \text{ mmol/L}$$

$$\text{MEFWC} = V\left(1 - 1.03[\text{Na}^+ + \text{K}^+]_{\text{urine}}/\left([\text{Na}^+]_{\text{p}} + 23.8\right)\right)$$

$$\text{MEFWC} = 2(1 - 1.03(50)/(125 + 23.8)) = 1.3 \text{ L}$$

Assuming that insensible water loss and fecal water loss approximate the water content of ingested food and water of oxidation [17], electrolyte-free water intake must be restricted to less than urinary MEFWC in order to achieve negative free water balance. Therefore, if the patient was placed on 1 L free water restriction, a negative free water balance of −0.3 L would be attained. In an attempt to increase the urinary electrolyte-free water clearance, the patient's daily solute intake was increased from 600 to 1,200 mOsm/day by increasing the patient's protein intake and Na^+ intake from 80 mmol/day to 200 mmol/day. Assuming that sodium handling was normal, urinary osmolality remained relatively fixed and daily urinary K^+ excretion remained the same:

$$\text{Urinary volume} = \text{solute excretion}/U_{\text{osm}} = 1{,}200/300 = 4 \text{ L/day}$$

Therefore,

$$\text{Urine } [\text{Na}^+] = 200/4 = 50 \text{ mmol/L}$$

$$\text{Urine } [\text{K}^+] = 20/4 = 5 \text{ mmol/L}$$

$$\text{MEFWC} = V\left(1 - 1.03[\text{Na}^+ + \text{K}^+]_{\text{urine}}/\left([\text{Na}^+]_{\text{p}} + 23.8\right)\right)$$

$$\text{MEFWC} = 4(1 - 1.03(55)/(125 + 23.8)) = 2.5 \text{ L}$$

Therefore, by placing the patient on a high protein and Na^+ intake, the same 1 L free water restriction would lead to a negative free water balance of −1.5 L (an increment of −1.2 L).

Alternatively, urinary electrolyte-free water clearance can also be increased with the utilization of vasopressin-2 receptor antagonist [19]. By antagonizing the action of ADH at the collecting tubule, vasopressin-2 receptor antagonist inhibits urinary reabsorption of free water, thus increasing urinary electrolyte-free water excretion. As vasopressin-2 receptor antagonist has little or no effect on urinary Na^+ and K^+ excretion, vasopressin-2 receptor antagonist increases urinary electrolyte-free water excretion in excess of electrolyte-free water intake, thereby resulting in

negative free water balance. Therefore, MEFWC is a useful clinical tool in quantifying the effectiveness of vasopressin-2 receptor antagonist in inducing urinary electrolyte-free water excretion.

Clinical Example

Patient is a 62-y.o. male who presented with hyponatremia secondary to SIADH. On initial presentation, plasma [Na^+] was 120 mmol/L, urinary osmolality was 800 mOsm/kg, urinary Na^+ excretion was 100 mmol/day, urinary K^+ excretion was 40 mmol/day, and daily solute excretion was 600 mOsm/day.

$$\text{Urinary volume} = \text{solute excretion}/U_{\text{osm}} = 600/800 = 0.75 \text{ L/day}$$

Therefore,

$$\text{Urine } [Na^+] = 100/0.75 = 133 \text{ mmol/L}$$

$$\text{Urine } [K^+] = 40/0.75 = 53 \text{ mmol/L}$$

$$\text{MEFWC} = V\left(1 - 1.03[Na^+ + K^+]_{\text{urine}}/\left([Na^+]_{\text{p}} + 23.8\right)\right)$$

$$\text{MEFWC} = 0.75(1 - 1.03(186)/(120 + 23.8)) = -0.25 \text{ L}$$

In this clinical setting where the urinary MEFWC was negative in value, urinary loss resulted in increased urinary electrolyte-free water reabsorption (rather than urinary electrolyte-free water excretion) which would actually lower the plasma [Na^+]. Therefore, any amount of electrolyte-free water intake would tend to lower the plasma [Na^+] in this patient. In such case, hyponatremia can only be corrected by increasing urinary electrolyte-free water excretion in excess of electrolyte-free water intake. The patient was therefore treated with a vasopressin-2 receptor antagonist, which resulted in a decrement in urinary osmolality to 100 mOsm/kg. Assuming that the daily Na^+, K^+, and solute excretion remained the same:

$$\text{Urinary volume} = \text{solute excretion}/U_{\text{osm}} = 600/100 = 6 \text{ L/day}$$

Therefore,

$$\text{Urine } [Na^+] = 100/6 = 17 \text{ mmol/L}$$

$$\text{Urine } [K^+] = 40/6 = 7 \text{ mmol/L}$$

$$\text{MEFWC} = V\left(1 - 1.03[\text{Na}^+ + \text{K}^+]_{\text{urine}}/\left([\text{Na}^+]_{\text{p}} + 23.8\right)\right)$$

$$\text{MEFWC} = 6(1 - 1.03(24)/(120 + 23.8)) = 5\ \text{L}$$

Importantly, this particular case illustrates the fact that free water restriction is ineffective in clinical settings where the urinary MEFWC is negative in value since any amount of electrolyte-free water intake would tend to lower the plasma [Na^+]. In such cases, the utility of vasopressin-2 receptor antagonist is required to increase the urinary electrolyte-free water excretion in excess of electrolyte-free water intake, thereby resulting in negative free water balance.

Conclusions

In summary, electrolyte-free water clearance is a simple clinical tool that can be utilized in the analysis and management of hyponatremia. In this chapter, we discussed the limitations of the classic FWC and EFWC formulas and the physiological basis behind the derivations of MEFWC and WB-EFWC. MEFWC is a more accurate tool for quantifying a defect in urinary free water excretion in hyponatremia. MEFWC and WB-EFWC are also helpful tools in defining the generation of the dysnatremias. In dilutional hyponatremia, MEFWC can also be used to determine the degree of free water restriction required to induce negative free water balance and to predict the effectiveness and feasibility of free water restriction as a treatment modality. Lastly, MEFWC is a useful tool in quantifying the effectiveness of an increment in daily solute intake as well as vasopressin-2 receptor antagonists in inducing urinary electrolyte-free water excretion.

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Chapter 4
Cerebral–Renal Salt Wasting

John K. Maesaka, Louis Imbriano, Shayan Shirazian, Nobuyuki Miyawaki, and Naveed Masani

Introduction

Cerebral salt wasting (CSW), or the preferred and more appropriate term, renal salt wasting (RSW), continues to be an ill-defined syndrome that requires clarification. Presently, there is general agreement that RSW does exist, but there is disagreement over its prevalence, generally considered to be common among neurosurgeons and the syndrome of inappropriate secretion of antidiuretic hormone (SIADH) to be more common than RSW among internists. This difference in estimating the prevalence of both disorders defines how difficult it is to differentiate RSW from SIADH. Resolution of this discrepancy becomes vital because of divergent therapeutic goals for both syndromes, to administer salt and water to volume-depleted patients with RSW, and to water-restrict water-loaded patients with SIADH. The awareness that even mild hyponatremia induces symptoms with potentially serious consequences has led to a tendency to treat all hyponatremic patients, thus introducing a therapeutic urgency to differentiate RSW from SIADH [1–9]. To add further uncertainty to this diagnostic and therapeutic dilemma are the recent reports of RSW occurring in patients without clinical cerebral disease [10, 11]. The term RSW will accordingly be used throughout this chapter instead of CSW. The approach to the diagnosis and treatment of hyponatremia can thus be considered to be in a state of flux. We intend to discuss the following in this chapter: (1) update the definition and pathophysiology of RSW, (2) how our inability to assess extracellular volume (ECV) accurately is at the root of the discrepancy over the relative prevalence of RSW and SIADH, (3) review the pertinent volume studies, (4) how to differentiate RSW from SIADH, (5) the emerging value of determining fractional urate excretion (FEurate) in RSW, SIADH, and reset osmostat (RO), (6) the

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probability that an increased FEurate with normonatremia is highly suggestive of RSW, (7) the existence of a natriuretic factor(s) in RSW, (8) suggest changing CSW to RSW and finally, (9) a normal FEurate in nonedematous hyponatremia identifies patients with RO and designate RO as a separate clinical entity from SIADH.

Definition and Pathophysiology of RSW

Our definition of RSW has been modified to: "ECV depletion due to inhibition of renal sodium transport by a circulating natriuretic factor that is associated with increased FEurate, normal renal, adrenal, and thyroid function with or without the following: high urinary sodium concentration (UNa), hypouricemia, presence of hyponatremia or cerebral disease" [12]. It appears that a disease entity usually involving the brain induces production of a natriuretic factor that decreases ECV by inhibiting renal sodium transport. The patient first enters a stage of negative sodium balance, which stimulates the renin–angiotensin–aldosterone system, reduces atrial/brain natriuretic peptide (A/BNP), alters glomerular hemodynamics, and possibly activates neural factors that attempt to decrease sodium excretion [13]. The volume-depleted subject must reach an equilibrated state, when sodium intake equals sodium excretion, to prevent total loss of body sodium and vascular collapse. Sodium excretion and UNa can thus be low, if sodium intake is low.

The magnitude of ECV depletion depends on the balance between the severity of renal sodium transport inhibition and sodium intake. Rarely, a combination of decreased sodium intake and substantial inhibition of renal sodium transport can lead to profound and symptomatic ECV depletion such as the development of postural hypotension, unsteady gait, and postural somnolence, dizziness, and slurred speech. More commonly, there is milder inhibition of sodium transport with near adequate salt intake to induce mild ECV depletion that would be difficult to detect by current methods of assessing ECV. There are, therefore, different degrees of volume depletion depending on the balance between the severity of sodium transport inhibition and salt and water intake, so the true prevalence of RSW cannot be determined until we improve our ability to assess ECV more accurately or develop better methods of differentiating RSW from SIADH.

In contrast to SIADH, when ADH production fails to respond to conventional volume and osmolar stimuli, there is appropriate stimulation of ADH secretion in RSW. The volume stimulus is more potent than the osmolar effect on ADH production, so the volume-depleted patient with RSW continues to secrete ADH despite a coexistent hypo-osmolality that would ordinarily inhibit ADH secretion [14]. This phenomenon is illustrated in our patient with RSW in whom saline resuscitation eliminated the volume stimulus for ADH production to allow the coexisting plasma hypo-osmolality to inhibit ADH production to indeterminate levels, thereby diluting the urine, and increasing free water excretion and serum sodium, Fig. 4.1 [10]. Determining whether the increase in plasma ADH is appropriate or inappropriate

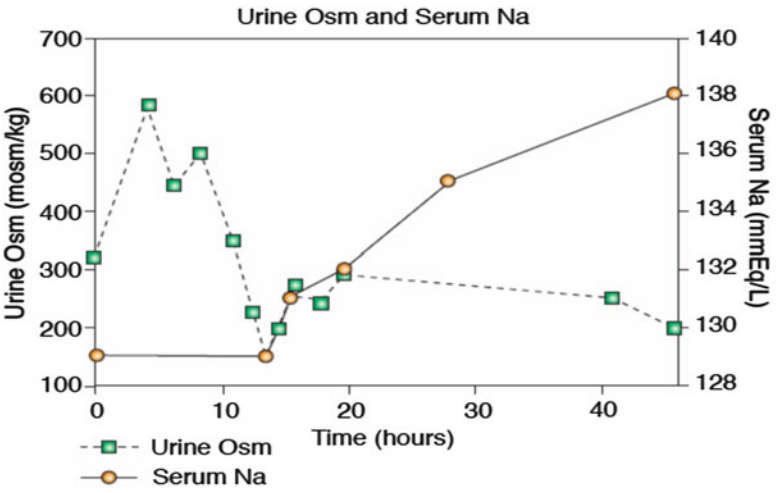


Fig. 4.1 Urine osmolality and serum sodium concentration during saline infusion at 125 ml/h. over 48 h period in volume-depleted hyponatremic patient with hip fracture. Note dilution of urine 13 h after initiation of saline, at which time a previously increased plasma ADH was not detectable, appropriate AD secretion [10]. See text. Reprinted with permission from Kidney International, Nature Publishing Group

Table 4.1 Laboratory and clinical features common to SIADH and RSW

Features common to SIADH and RSW
• Association with intracranial diseases
• Hyponatremia
• Concentrated urine
• Urinary [Na] usually $>$ 20 mEq/L
• Normal renal/adrenal/thyroid function
• Nonedematous
• Hypouricemia, Increased FEurate
• Only difference is volume status

depends on our ability to assess ECV accurately, because overlapping presentations make it difficult to differentiate SIADH from RSW, Table 4.1. Both syndromes tend to be associated with intracranial diseases, have a concentrated urine with UNa usually exceeding 20 mmol/L, have hypouricemia and increased fractional excretion (FE) of urate, Table 4.1. The only difference on first encounter with the patient is their state of ECV, which is impossible to assess by usual clinical criteria and is largely responsible for the disagreement over the prevalence of RSW and SIADH [10, 15–17].

Patients with SIADH undergo a similar sequence of negative sodium balance followed by sodium equilibration [18]. In contrast to RSW, the increase in water reabsorption maintains a high ECV that increases A/BNP and decreases plasma renin and aldosterone, which under ideal conditions can help to differentiate RSW from SIADH [11, 19, 20]. Data in well-documented cases of RSW reveal plasma

renin to be increased or normal while on a low or normal salt diet, respectively, while a more consistent increase in plasma aldosterone appears to reflect their volume-depleted state [10, 11].

It is important at this juncture to review briefly salt balance and the important contributions made by the kidneys in maintaining ECV. The kidneys appear to have an innate sense of what ECV should be and maintain ECV within narrow limits by activating or inhibiting factors that increase or decrease sodium excretion [21]. It is evident from studies in Yanomamo Indians, the "no salt society," that sodium requirements to maintain normal ECV are virtually zero [22]. Their mean serum sodium was 140 mmol/L, urine volume 1 L per day, urine sodium output 1 mmol per day, and blood pressure 102/62 mmHg. When normal subjects are in negative sodium balance, urine sodium output per day decreases to very low levels and does not increase until their sodium losses have been replaced or exceeded [21, 23, 24]. Normal kidneys can, thus, maintain a normal ECV with virtually no salt intake [21, 22]. Maintaining a normal ECV, however, is not instantaneous because a normal subject who acutely reduces and maintains a low sodium intake remains in positive sodium balance for 3–5 days before reaching equilibrium at the lower salt intake [25].

Assessment of Extracellular Volume

There is agreement that the assessment of ECV by clinical criteria is fraught with inaccuracies [10, 15–17]. The usual criteria of tissue turgor, axillary sweat, dry mucus membranes, flattened neck veins, or even postural hypotension in a nonedematous patient have been collectively inaccurate in assessing ECV. Even the presence of postural hypotension must consider autonomic dysfunction as we reported in a patient with autonomic failure and SIADH, who had increased blood volume by radioisotope-dilution methods and depressed plasma renin and aldosterone [11].

Other noninvasive and invasive methods have also been limited by various factors. Central venous pressures (CVP) have a poor correlation with concomitant radioisotope-dilution measurements of blood volume and have been discarded as a guide to fluid management [26]. Bioimpedance is not useful as a single determination, and pulmonary wedge pressures are not only limited by a failure consistently to predict ECV but also by their invasiveness [27, 28]

There are two methods that reliably determine ECV with greater accuracy. One is the gold standard radioisotope-dilution method, using radioiodinated serum albumin (RISA) and/or 51 chromium-labeled red blood cells (^{51}CrRBC), and the other, determination of total body water by deuterium and extracellular water by sodium bromide. There are a limited number of studies using radioisotope-dilution methods and none measuring total and extracellular water.

Volume Studies Using Radioisotope-Dilution and Other Pertinent Methodologies

As discussed earlier, the overlapping similarities in some of the common features that are noted in RSW and SIADH remains a continuing obstacle to differentiate one syndrome from the other, Table 4.1. The original report of salt wasting in 1950 lacked supporting data to prove cerebral or RSW in three patients [29]. In 1954, Cort proved the existence of RSW by demonstrating a decreased ECV by measuring chloride space and demonstrating a prolonged period of negative sodium balance that would be accepted as salt wasting [30].

Because of the importance of accurately assessing ECV in RSW and SIADH, we will review some of the pertinent studies that have been reported. Blood volume studies have been reported in four studies of neurosurgical patients, using RISA and/or ^{51}CrRBC. A study of 12 neurosurgical hyponatremic patients with UNa ranging from 41 to 203 mmol/L determined blood volume by RISA and ^{51}CrRBC. Of the 12 patients, blood volumes were decreased in 10 and increased in 2 as compared to 6 control patients [31]. Because a volume depleted subject with normal kidneys would have very low UNa, the UNa of 41–203 mmol/L was consistent with RSW; thus, of the 12 patients 10 or 83.3 % had RSW and 2 or 16.7 % had SIADH. Eight of the 12 patients had subarachnoid hemorrhage (SAH) [31]. In a study of 21 patients with SAH, blood volume decreased in 8 of 9 hyponatremic patients and increased in only 1, suggesting that 88.9 % had RSW and 11.1 % had SIADH. In 12 normonatremic patients with SAH, plasma volume decreased in 8 and increased in 4, suggesting that RSW occurred in 66.7 % without hyponatremia. All volume depleted hyponatremic and normonatremic patients were in negative sodium balance. UNa was not reported in these patients [32]. RSW can, thus, occur without hyponatremia and is a common perception today [12, 16, 33]. In a study of 18 hyponatremic neurosurgical patients with diverse brain pathology, 17 had decreased blood volume by ^{51}CrRBC and all 18 had decreased CVP. UNa ranged from 43 to 210 mmol/L and the hyponatremia corrected within 72 h after initiating saline infusion. This is consistent with saline infusions correcting the hyponatremia within 48 h in well-documented cases of RSW as compared to no correction in SIADH [10, 11]. They concluded that all 18 patients had RSW [34].

A study in neurosurgical patients determined blood volume by ^{51}CrRBC in 20 hyponatremic and 20 nonhyponatremic "control" patients. All hyponatremic patients met criteria for SIADH [35]. The exclusion of patients demonstrating evidence of "dehydration or hypovolemia" represents a flaw that would tend to exclude hypovolemic patients with RSW, being aware, however, of our inability to assess ECV accurately. An additional flaw in the design of this study was the selection of the control and experimental groups of patients. Both groups were hypouricemic and had increased FEurate of >10 %. As will be discussed below, there is ample evidence to suggest that the normonatremic control group with hypouricemia and increased FEurate could consist of true normal controls and RSW, depending on their FEurate, Fig. 4.2a, b. On the other hand, the hyponatremic

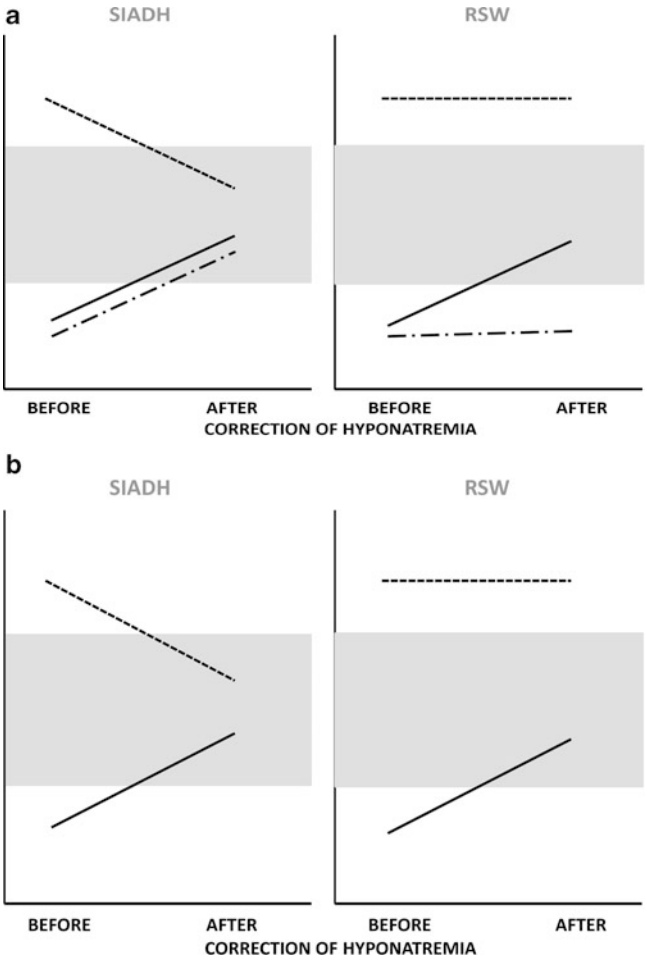
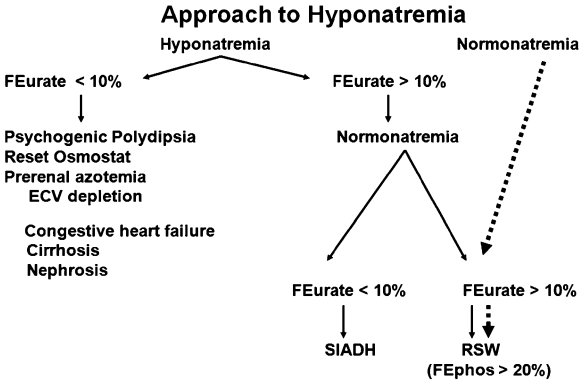


Fig. 4.2 Relationship between FEurate (FEUA), serum urate (SUA), and serum sodium (SNa) before and after correction of hyponatremia in SIADH and RSW. *Shaded areas* represent normal ranges. Note normalization of FEurate in SIADH and persistence of increased FEurate after correction of hyponatremia in (**a, b**). Figure **b** eliminates SUA, see text [56]. Figure **a** reprinted from American Journal of Kidney Diseases, with permission from Elsevier. Figure **b** reprinted from Maesaka J, Imbriano L, Shirazian S, Miyawaki N. Complexity of differentiating cerebral–renal salt wasting from SIADH, emerging importance of determining fractional urate excretion. In: Vijayakumar S, editor. Novel Insights on chronic kidney disease, acute kidney injury and polycystic kidney disease. Croatia: InTech; 2012. p. 41–66, with permission from InTech

group with hypouricemia and increased FEurate could have been composed of patients with RSW and SIADH, Fig. 4.2a, b, Table 4.2. Although blood volumes were comparable in the "control" and hyponatremic groups, the flaws in the design of this study mitigate against any meaningful conclusions as they relate to SIADH and RSW in neurosurgical patients [35].

Table 4.2 New algorithm to evaluate patients with hyponatremia based on central role of FEurate



Note absence of volume status other than edematous (hypervolemic) states and UNa. Normonatremia and FEurate without hyponatremia (connected by dotted lines) needs further verification, dotted line. (Reprinted from Maesaka J, Imbriano L, Shirazian S, Miyawaki N. Complexity of differentiating cerebral–renal salt wasting from SIADH, emerging importance of determining fractional urate excretion. In: Vijayakumar S, editor. Novel Insights on chronic kidney disease, acute kidney injury and polycystic kidney disease. Croatia: InTech; 2012. p. 41–66, with permission from InTech)

In other pertinent studies, ten hyponatremic patients with acquired immune deficiency syndrome (AIDS) had saline-responsive postural hypotension, increased plasma renin and aldosterone levels, hypouricemia, increased FEurate and UNa >40 mmol/L, and CVP determinations of 0 cm water (admittedly problematic) that collectively supported the diagnosis of RSW [36, 37].

Two other studies deserve comment to bring clarity to the confusion that exists in the literature. In a retrospective study of 319 patients with SAH, 179 were hyponatremic and met criteria for SIADH and CSW. The volume status was determined by unacceptable CVP determinations, hypotension, and other undefined parameters. They found that 69.2 % had SIADH, 6.5 % CSW and 4.8 % a combination of SIADH and CSW [38]. In a similar retrospective study, they found 62 % to have SIADH, 26.7 % hypovolemia, 16.6 % drug-related, 4.8 % CSW, 3.7 % related to IV fluids, and 2.7 % a combination of CSW and SIADH. The combination of SIADH and CSW occurring in the same patient lacked supportive data to justify an extremely difficult and improbable diagnostic combination, especially in a retrospective study [38, 39]. The neurosurgical studies demonstrate by gold standard methods of determining ECV, that RSW is much more common than SIADH in neurosurgical patients, especially SAH.

Emerging Value of Determining FEurate

The coexistence of hyponatremia, hypouricemia, and increased FEurate in SIADH was first described in 1971 [40]. There was a unique relationship between FEurate and serum sodium, FEurate being increased when the patient was hyponatremic and normalizing with correction of hyponatremia [40]. Eight years later Beck duplicated these findings by noting normalization of a previously increased FEurate with correction of hyponatremia by water restriction and except for one overlapping value, there was complete separation between the mean serum urate of 2.9 mg/dL in SIADH and 7.9 mg/dL in other causes of hyponatremia [41]. This led to the recommendation that the coexistence of hyponatremia and hypouricemia, defined as <4 mg/dL, identified patients with SIADH as compared to most other causes of hyponatremia [41]. Others found a consistent decrease in serum urate in SIADH with virtually no or partial overlap in serum urate between SIADH and other causes of hyponatremia [42–46]. Several studies also demonstrated normalization or reduction of a previously increased FEurate after correction of hyponatremia by water restriction, Fig. 4.2a [40–42, 44, 45]. Improvement in hypouricemia and normalization of a previously increased FEurate after correction of hyponatremia appear to be characteristic findings in SIADH. As will be discussed later, hypouricemia has not been found to be as useful as FEurate, Fig. 4.2a, b.

In contrast to a characteristic normalization of FEurate with correction of hyponatremia in SIADH, we reported a persistently increased FEurate after correction of hyponatremia by water restriction in five patients with normal renal, adrenal, and thyroid function, suggesting that these patients were pathophysiologically different from SIADH [47]. Our insight case of metastatic pancreatic carcinoma had no evidence of cerebral disease but presented with findings that were distinctly different from SIADH. He had edema, ascites, serum albumin 1.5 g/dL, hypouricemia, serum urate 1.1 mg/dL, increased FEurate 34.2 %, hypophosphatemia, phosphorus 1.7 mg/dL, increased FEphosphate 29.1 %, UNa 99 mmol/L, Uosm 716 mosm/kg, and a persistently increased FEurate of 30 % after correction of hyponatremia by water restriction. He had normal renal, adrenal, and thyroid function and his edema, ascites, hypoalbuminemia, hypophosphatemia, increased FEphosphate, and persistently increased FEurate after correction of hyponatremia by water restriction were collectively inconsistent with SIADH. We interpreted these findings to be a variant of the Fanconi syndrome with defects in proximal tubule transport of multiple solutes [47]. The second insightful and instructive case was a patient with bronchogenic carcinoma and negative CT scan of brain, who presented with hyponatremia, saline-responsive postural hypotension, and tachycardia that were consistent with ECV depletion. His serum sodium of 116 mmol/L and postural hypotension and tachycardia responded to large volumes of saline with serum sodium increasing from 116 to 121 mmol/L. The baseline Uosm was 323 mosm/kg and UNa 42 mmol/L, but the serum urate of 2.0 mg/dL and increased FEurate of 26.5 % in the absence of cerebral disease convinced the internist that we were dealing with a patient with SIADH and was fluid-restricted. The patient progressively decreased his weight, developed postural hypotension, anorexia,

weakness, and postural unsteadiness in gait, somnolence with closing of eyelids, and slurred speech. His serum sodium finally corrected to 138 mmol/L on a fluid-restricted and heavily salt-supplemented diet at which time the FEurate remained surprisingly increased at 14.7 %, despite evidence for significant ECV depletion. At this time, his Uosm was 980 mosm/kg, UNa 181 mmol/L, and he remained hypouricemic with a serum urate 2.2 mg/dL. He responded well to saline therapy with reversal of all his symptoms. This case confirmed our notion that a persistently increased FEurate after correction of hyponatremia represented a group that was pathophysiologically different from SIADH and was consistent with RSW. The normal CT scan of brain also supported our evolving realization that RSW can occur without cerebral disease [47]. We found a persistent increase in FEurate and hypouricemia after correction of hyponatremia in three additional cases, one with bronchogenic carcinoma that had metastasized to brain, another with disseminated Cryptococcus that involved brain and uncomplicated Hodgkins disease with no clinical cerebral disease [47]. Except for the persistent increase in FEurate, the hyponatremia, high UNa, and concentrated urine were consistent with SIADH in all of these patients. We felt that these patients were pathophysiologically different from SIADH and the increased FEurate with normonatremia might differentiate RSW from SIADH, Fig. 4.2a, b. The absence of clinical cerebral disease in three of five patients suggested that CSW might be an inappropriate and restrictive designation.

We extended our study of urate metabolism in hyponatremic patients by prospectively evaluating 96 patients, who met criteria for a diagnosis of AIDS. Sixteen patients had combined hyponatremia and hypouricemia and of 23 patients studied, 21 were hypouricemic, 19 had increased FEurate >10 %, and all hyponatremic patients had UNa >20 mmol/L and concentrated urines that were consistent with SIADH and RSW. Evidence for RSW was noted in ten hyponatremic patients who had saline responsive postural hypotension, CVP of 0 cm water, hyponatremia, hypouricemia, increased FEurate, increased plasma renin and aldosterone, high UNa, and concentrated urine that were consistent with RSW [36, 37]. In order to strengthen our growing interest and belief that an increased FEurate in the presence of normonatremia or after correction of hyponatremia was consistent with RSW, we decided to investigate patients with neurosurgical diseases to determine how urate would be handled in a group of patients that was known to have a high incidence of RSW [31, 32, 34, 48]. We prospectively studied 29 patients with neurosurgical diseases of multiple etiologies and 21 age and gender-matched controls. Seven were hypouricemic, defined as serum urate <3 mg/dL, 18 had increased FEurate, and only one patient was hyponatremic [48]. The increased FEurate with normonatremia provided additional support of our previous proposal that this combination might be consistent with RSW. Our findings were consistent with the frequency with which RSW was noted in neurosurgical patients and was further supported by demonstrating natriuretic activity in the plasma of these patients when their plasma was injected into rats, vide infra [31, 33, 34, 49]. These observations suggest that an increased FEurate with normonatremia is consistent with RSW without a need to correct a previous hyponatremia, Fig. 4.2a, b, Table 4.2. We decided to test the relationship between an increased FEurate and normonatremia

by investigating patients with Alzheimer's disease (AD) who reported to have low serum urate. [50] and: In a study of AD, multi-infract dementia (MID), and normal age and gender-matched controls, we found 18 AD patients to have significantly higher mean FEurate and lower mean serum urate than 6 with MID and 11 controls [51]. It was not surprising to note only 1 AD patient was hyponatremic since these patients would be expected to decrease water intake because of the thirst defect of aging and dementia. Demonstration of natriuretic activity in the plasma of these AD patients as compared to MID or controls further supported our notion that a normonatremic patient with increased FEurate might be consistent with RSW [51].

The unpredictability and difficulty in correcting hyponatremia by fluid restriction and salt supplementation hampered our effort to test our proposal that a persistently increased or normalization of FEurate after correction of hyponatremia could be used to differentiate RSW from SIADH. The predictable correction of hyponatremia by V1/V2 ADH receptor blockers could not be used for this purpose because they are contraindicated in volume-depleted patients [2]. We decided to expand the suggestion to administer hypertonic saline to treat symptomatic hyponatremia with cerebral diseases regardless of whether or not they had SIADH or RSW [52, 53]. We corrected the hyponatremia of patients with increased FEurate with 1.5 % saline and determined whether FEurate would normalize as in SIADH or remain persistently increased as in RSW, Fig. 4.2a, b. Serum sodium increased to >138 mmol/L within 3 days with 1.5 % saline and FEurate normalized in two patients who met criteria for SIADH [54]. The decrease in FEurate from 27.5 to 8.5 % in one patient confirmed our impression that saline has a meager effect on FEurate and the infusion of 1.5 % saline can be used to differentiate SIADH from RSW by determining whether FEurate normalizes or remains increased after timely correction of hyponatremia, Fig. 4.2a, b. The rate of correcting the hyponatremia can be controlled by adjusting water intake and/or rate of infusion of 1.5 % saline, being mindful that the patient has adequate cardiac function.

Studies to Introduce New Directions in RSW and SIADH

Renal Salt Wasting Without Clinical Evidence of Cerebral Disease: Consider Changing CSW to RSW

Although three of our five original cases of probable RSW had no clinical evidence of cerebral disease, we were unwilling to propose changing CSW to RSW until we had incontrovertible evidence of RSW occurring in a patient without cerebral disease [10, 11]. One very instructive case was a hyponatremic patient with a hip fracture, who was initially water-restricted for 7 days for an erroneous diagnosis of SIADH. While being water-restricted, her Uosm was 362 mosm/kg and UNa only 6 mmol/L, which was initially thought to be consistent with hypovolemic hyponatremia of the prerenal type with normal renal function [10]. A low serum urate of 3.4 mg/dL, however, was

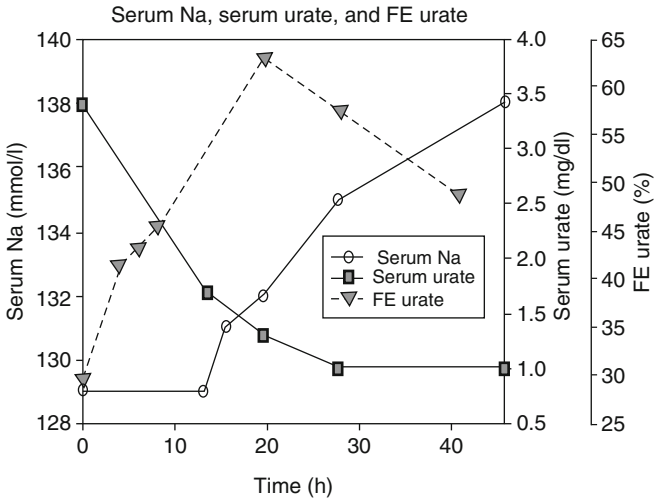


Fig. 4.3 Relationship between serum urate, serum sodium, and FEurate during volume repletion with saline for 48 h. Note the persistence of increased FEurate after correction of hyponatremia contrasts to SIADH. Note: saline has a meager effect on FEurate, Table 4.2 [10]. Reprinted with permission from Kidney International, Nature Publishing Group

not consistent with prerenal azotemia and more consistent with SIADH and RSW. A volume-depleted patient with normal renal function would be expected to have a higher serum urate and FEurate below 3 % [55]. Based on this reasoning, we determined blood volume by RISA and ^{51}CrRBC and started saline infusion after obtaining baseline studies. The FEurate was markedly increased at 29.6 %, which was consistent with both SIADH and RSW, but a 7.1 % reduction in blood volume, increased plasma renin and aldosterone, and low normal plasma ANP collectively supported the diagnosis of RSW [10]. The UNa of 6 mmol/L was attributed to weakness, anorexia, and reduced salt intake while being fluid-restricted to 750 ml/day for 7 days prior to our studies. She felt stronger with increased appetite approximately 18 h after initiating saline infusion. The UNa of 6 mmol/L proves that an equilibrated salt waster can have a low UNa if salt intake is low. Moreover, saline infusion progressively diluted the urine to a Uosm of 152 mosm/kg 13 h after initiating saline therapy, at which time plasma ADH decreased from a baseline of 1.9 pg/mL to indeterminate levels. The elimination of the volume stimulus for ADH secretion by saline allowed the coexisting plasma hypo-osmolality to inhibit ADH secretion, increase free water excretion as dilute urines, and increase serum sodium from a baseline 120–138 mmol/L within 48 h after initiating saline infusion, Fig. 4.1 [10]. Interestingly, the baseline FEurate of 29.6 % increased further to a peak of 63 and 48 % at the time of correction of the hyponatremia to138 mmol/L, Fig. 4.3. The effect of saline on FEurate has been amply shown to be minimal and the persistently increased FEurate after correction of hyponatremia is consistent with RSW and not SIADH [56–59]. In our view, this very instructive case illustrates all of the physiologic parameters for RSW and proved unequivocally the existence of RSW. The decrease

in blood volume as determined by radioisotope-dilution methods, increased plasma renin and aldosterone, low normal plasma ANP, appropriately increased plasma ADH, which was inhibited by the combination of volume repletion and plasma hypo-osmolality, increased free water excretion, timely correction of hyponatremia, and persistently increased FEurate after correction of hyponatremia collectively prove the existence of RSW and illustrate the unique characteristics of RSW. We also reported a similar case of RSW without cerebral disease in a patient with pneumonia. He had a concentrated urine, UNa of 39 mmol/L, hypouricemia, increased FEurate, increased aldosterone but normal plasma renin as explained above, dilution of urine 14 h after initiation of saline infusion, and correction of hyponatremia within 48 h after initiation of saline infusion [11].

The persistently increased FEurate after correction of hyponatremia in these two cases of unequivocal RSW supports our contention that a persistently increased FEurate after correction of hyponatremia or possibly the coexistence of increased FEurate and normonatremia without a previous hyponatremia is consistent with RSW [12, 56, 60]. These reports prove that RSW does exist, can occur without evidence of clinical cerebral disease, can have a low UNa if salt intake is low, and have a persistently increased FEurate [10, 11]. The two cases of RSW without cerebral disease allowed us to suggest that CSW is an outmoded and inappropriate term that should be changed to RSW [10–12]. This change has practical value because RSW would not be considered if there is no evidence of cerebral disease.

Although RSW might be rare in diseases not involving the brain, the prevalence of RSW in this group of patients has yet to be determined. The volume studies reviewed earlier suggest that RSW is more common than SIADH in neurosurgical patients. Until we determine the true prevalence of RSW in patients with and without clinical cerebral disease and improve methods to differentiate SIADH from RSW, we will continue to mismanage these patients. Although the increased morbidity and mortality associated with this inappropriate treatment has been documented in the literature in isolated instances, it is probably much more common than we realize [10, 47, 61, 62]. It is well known that fluid restriction of hyponatremic patients with SAH who were misdiagnosed as SIADH instead of RSW increased morbidity and mortality rates that were attributed to decreased brain perfusion and extension of ischemia and infarction [62].

We hope changing CSW to RSW is one important step toward a better understanding and approach to an enigmatic syndrome that will improve outcomes in the future.

Hyponatremia with Normal FEurate Identifies Patients with Reset Osmostat

As part of the emerging value of determining FEurate in hyponatremic conditions, it would be appropriate to review briefly how a normal FEurate appears to identify patients with reset osmostat (RO). RO is a common disorder that is classified as type C SIADH [63]. It is characterized by: euvolemia with normal renal, adrenal, and

thyroid function, hyponatremia resulting from stimulation of ADH secretion at a lower plasma osmolality or RO, a reasonably normal diluting and concentrating capacity of urine, and maintaining normal sodium balance without correcting serum sodium [64] Because it has been difficult to treat the usually mild hyponatremia, the previous recommendation of not treating the hyponatremia of RO has been challenged by recent recommendations to treat virtually all hyponatremics, thus, creating a therapeutic dilemma [5–9, 65–68]. In our study, every hyponatremic patient with normal FEurate had RO as determined by a random Uosm <200 mosm/kg in 8 patients and after a normal water-loading test in 6 patients, regardless of UNa or serum urate [69]. The undetectable plasma ADH levels in four patients studied during the water-loading test were consistent with RO. Eight patients were hypouricemic, yet all had a normal FEurate [69]. A normal FEurate in a nonedematous hyponatremic patient with a randomly collected dilute urine appears to be highly consistent with RO. In the absence of a dilute urine, however, we do not recommend performing a water-loading test to prove the diagnosis of RO and to treat the patient as for SIADH. Treatment of comorbid conditions can improve or normalize the osmostat. We concluded that RO occurs commonly, a normal FEurate in a nonedematous hyponatremic patient is highly suggestive of RO, and FEurate is superior to serum urate in hyponatremia [56, 69]. These studies also suggest that RO is pathophysiologically different from the more traditional subtypes of SIADH by virtue of the normal FEurate and predictability of ADH responses to plasma osmolality. We would, therefore, like to suggest designating RO as a separate clinical entity and not as type C SIADH.

Determination of FEurate is Superior to Serum Urate

Our recent studies refine the proposal by Beck that the coexistence of hyponatremia and hypouricemia differentiates SIADH from most other causes of hyponatremia [41]. Our studies prove FEurate to have greater importance than serum urate, as we have reported increased FEurate with serum urate > 5 mg/dL and normal FEurate with hypouricemia [36, 48, 69]. The largely arbitrary definition of hypouricemia that varies between 1.5 and 4 mg/dL reflects an inadequate understanding of what controls serum urate levels as compared to well-defined parameters that have been established for FEurate [41, 56, 70]. In our view, determining FEurate has much greater value than serum urate.

Natriuretic Factor(s) in RSW

A/BNP has been cited as a possible cause of salt wasting in RSW [71, 72]. A/BNP is increased in subarachnoid hemorrhage (SAH) [73], a condition with a high prevalence for RSW, but it is also increased in a nonsalt wasting syndrome such as

SIADH and salt-retaining states such as congestive heart failure. The low normal ANP in our unequivocal case of RSW is consistent with volume depletion and thus, an unlikely cause of RSW [10].

Clearance studies were performed in rats infused with plasma of same patients with neurosurgical disease and AD with increased FEurate and normonatremia and of age and gender-matched controls with normal FEurate and normonatremia that was reviewed earlier. Glomerular filtration rates and blood pressures were comparable in all studies. FElithium increased from 22.3 to 27.2 % in control rats to 36.6–41.7 % in rats infused with plasma of neurosurgical disease and AD, respectively [49, 51]. FENa increased significantly from 0.3 to 0.33 % in control animals to 0.50–0.63 % in neurosurgical disease and AD, respectively [49, 51]. Because lithium is transported on a one-to-one basis in the proximal tubule with little or no transport in the distal nephron, the increase in FElithium suggests that the major site of natriuretic activity is in the proximal tubule [74, 75]. It is highly unlikely that the natriuretic factor in RSW is A/BNP because of differences in their physiologic characteristics and low levels plasma A/BNP in RSW [76, 77].

Diagnostic Approach to Hyponatremia and Differentiating SIADH from RSW

The traditional approach to the evaluation of a hyponatremic patient is to determine whether or not the patient is euvolemic, hypovolemic, or hypervolemic. As stated above, this scheme has serious practical limitations because we are unable to distinguish the euvolemic from the hypovolemic patient. UNa also has limited value because it is complicated by many factors, such as diuretics, the acutely vomiting patient with bicarbonaturia, acute and chronic kidney diseases, and low UNa in the patient with SIADH and RSW on a low sodium diet. Limitations of UNa in the evaluation of patients with hyponatremia have also been noted by others [17].

Under ideal conditions, plasma renin and aldosterone can help to differentiate SIADH from RSW, being decreased in SIADH and increased in RSW, although renin can vary depending on salt intake as discussed above. Aside from the inordinate delay in reporting values by several days, plasma renin and aldosterone have limited value because they are unfortunately affected by other factors, such as the frequent use of ACE inhibitors, ARBs, diuretics, NSAIDS, saline infusions, and heparin [77, 78]

BNP has been used as a volume marker, being increased in volume expanded states such as heart failure and SIADH and decreased in hypovolemic states such as RSW, but has not been systematically studied in SIADH and RSW.

It appears that the determination of ECV, UNa, plasma renin, aldosterone, and BNP has limited value in assessing hyponatremia. We are still unable to establish the diagnosis of RSW or SIADH on first encounter with the patient. It is apparent that our current approach to the evaluation of a hyponatremic patient has proven to

be inadequate, and it is a good time to find newer approaches that will lead to a better understanding of hyponatremia and outcomes. To this end, we are in agreement with Moritz to question the validity of the subtyping of SIADH [33]. Moritz proposes that type B SIADH could be consistent with RSW and our recent findings in RO demonstrate RO to be pathophysiologically different from SIADH by virtue of having a normal FEurate and predictable ADH response to changes in plasma osmolality [33, 63, 69]. Both arguments can be supported by credible explanations and should be the subject of future investigations.

Based on a large body of accumulated data and experience with the utilization of serum urate and FEurate in hyponatremic patients, we would like to propose an algorithm based on FEurate, Table 4.2. This algorithm eliminates the need to determine UNa, plasma/serum levels of urate, renin, aldosterone, or BNP, or to assess ECV except to note the presence or absence of edema and/or ascites such as heart failure, cirrhosis, or nephrosis. Renal failure, thyroid or adrenal insufficiency, and drugs that induce hyponatremia should be considered. In our experience, this algorithm has proven to be superior to existing approaches to evaluating the hyponatremic patient. If FEurate is 5–10 %, we must consider psychogenic polydipsia and RO, being mindful that edematous states such as congestive heart failure, cirrhosis, nephrosis, or preeclampsia can be readily identified. The hypovolemic patient with normal kidney function would be expected to have a low FEurate because of their prerenal state and might be the most difficult differential to make in this group, but the low mean FEurate of 2.85 %, increased serum urate, and low UNa might collectively help to differentiate this group from RO [13, 59]. Psychogenic polydipsia can be differentiated from RO by the history of excessive water intake and very dilute urines [79]. RO makes up the largest group of hyponatremic patients with FEurates between 5 and 10 % as discussed above. It should be pointed out that we have had difficulty establishing the normal limits for FEurate, realizing that the normal range will probably be established at 4–11 % rather than 5–10 %. In the nonedematous hyponatremic patient with a normal FEurate, we suggest a diligent search for randomly excreted dilute urines to make the diagnosis of RO. In the absence of a randomly collected dilute urine, we do not recommend performing a water–loading test to prove the diagnosis of RO but to treat the patient as for SIADH [69].

FEurate >10 % or preferably >12 % has been largely reported in patients with SIADH and RSW. FEurate can be used to differentiate SIADH from RSW by correcting the coexistent hyponatremia and noting whether FEurate normalizes as in SIADH or remains persistently increased as in RSW, Fig. 4.2a, b. Hydrochlorothiazide-induced hyponatremia has FEurates that are similar to SIADH but can be readily ruled out by noting correction of hyponatremia after discontinuing the diuretic [80]. Although neurotropic drugs have been reported to induce an SIADH-like picture, FEurate has not been studied in this group of patients.

Because it has been difficult to correct hyponatremia by fluid restriction and salt supplementation, we would consider correcting the hyponatremia with hypertonic saline in 2–3 days in the appropriate patient and determine whether FEurate would

correct as in SIADH or remain increased as in RSW, Table 4.2 [54]. The dotted lines in Table 4.2 connecting normonatremia, increased FEurate, and RSW represent the unresolved probability that an increased FEurate with normonatremia would be consistent with RSW. While there are supporting data to suggest this to be a valid conclusion, there is general agreement that RSW occurs without hyponatremia and the increased FEurate might alert us to RSW. Future studies will hopefully provide further insights into this relationship. It is our hope that other investigators will utilize FEurate to determine its efficacy in the evaluation of hyponatremic patients.

Treatment of RSW

The treatment of RSW is simple. Saline is the appropriate therapy that will reverse the sequence of pathophysiologic events that compensate for the inhibition of renal sodium transport, Fig. 4.1 [10, 11]. The major obstacle to implementation of this therapeutic maneuver, however, is an accurate diagnosis of RSW. Resolution of the dilemma of differentiating SIADH from RSW will eliminate the increase in morbidity and mortality resulting from fluid restriction in a patient with RSW for an erroneous diagnosis of SIADH [10, 47, 61, 62]. Moreover, the awareness that symptoms are now being attributed to even mild hyponatremia not only sheds light on a long unrecognized phenomenon but introduces some urgency in developing treatment strategies for hyponatremia with diverse etiologies and divergent therapeutic goals. Treatment, however, has undergone a period of uncertainty due to adverse outcomes that are related to delays in treatment and over-correction of chronic hyponatremia [72]. A more comprehensive review of the treatment modalities will be covered in a separate chapter. It is, however, relevant to remind the reader of circumstances covered in this chapter that might contribute to an improved diagnostic and therapeutic approach. The use of the V1 and/or V2 ADH receptor blockers is contraindicated in patients with RSW [2]. In this regard, we must be cautious in using this class of drugs in patients with coexisting hyponatremia and increased FEurate before differentiating SIADH from RSW, since RSW can occur in patients without cerebral disease, Table 4.2. The V1/V2 ADH receptor blockers have proven to be effective in patients with hypervolemic hyponatremia and in our view can be used in patients with hyponatremia and normal FEurate where RO would be the most likely diagnosis. While the rationale for increasing salt and water intake in patients with RSW is obvious, we are in complete agreement with the recommendation to utilize hypertonic saline to hyponatremic patients with cerebral diseases to avoid damages incurred by the hypo-osmolality of serum and to treat a group of patients in whom RSW is much more common than SIADH [33, 52, 53]. This maneuver also eliminates the possibility of creating desalination in patients with RSW and SIADH when serum sodium decreases with administration of normal saline because urinary sodium concentration is higher than the sodium concentration in the input fluid [33, 81].

Administration of saline not only prevents hyponatremia from occurring, but an increased FEurate associated with normonatremia could be a justification to continue saline regardless of whether or not they have cerebral disease because of the probability of RSW [33, 52, 81, 82]. Hypertonic saline appears to be the treatment of choice in hyponatremic patients with intracranial diseases regardless of etiology and has even been advocated as a first line of therapy for hyponatremia [33, 52]. These evolving therapeutic options raise interesting questions whether hypertonic saline should be routinely administered to patients with increased FEurate and hyponatremia with or without cerebral disease, when the diagnostic possibilities include RSW and SIADH. Hypertonic saline in this setting has an added benefit by being able to correct and treat the hyponatremia within 2–3 days with less effect on expanding ECV than isotonic saline, making note whether FEurate remains persistently increased as in RSW or normalize as in SIADH after correction of hyponatremia, and determine future therapy depending on outcome, Fig. 4.2a, b. It is anticipated that these questions will be resolved in future studies that will address the diagnostic and therapeutic challenges discussed in this chapter.

Summary

The present chapter hopefully clarified the present diagnostic and therapeutic dilemma that exists for SIADH and RSW. We hope we provided an objective review of the complexity of differentiating SIADH and RSW, the discrepancy in the literature over the relative prevalence of SIADH and RSW, and why RSW should be considered to be much more common than SIADH in neurosurgical diseases. We hope that we have emphasized (1) our inability to assess the state of ECV. (2) RSW is much more common than SIADH in neurosurgical patients. (3) RSW does exist. (4) A natriuretic factor is present In RSW and is not A/BNP. 4. RSW should replace CSW because RSW can exist without clinical cerebral disease. (5) FEurate can help differentiate SIADH from RSW. (6) FEurate is superior to serum urate in evaluating hyponatremic patients. (7) A normal FEurate in a nonedematous hyponatremic is very consistent with RO. (8) RO should be eliminated as a subtype of SIADH. (9) Increased FEurate with normonatremia is consistent with RSW, but future studies must determine whether it is diagnostic of RSW. Finally we advocate a broader use of FEurate in the evaluation of hyponatremia.

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Chapter 5
CNS Manifestations of Hyponatremia and Its Treatment

Fabrice Gankam Kengne and Guy Decaux

Introduction

Hyponatremia is the most frequent electrolyte disorder encountered in clinical practice [1–5]. Depending on the cut-off, the subset of the population studied and their comorbidities, the rough prevalence of hyponatremia varies from 15 to 30 % in the hospital as opposed to 4.7 % in the community. The extracellular sodium is the principal determinant of the extracellular osmolarity and because the osmolarity of the extracellular fluid is a crucial determinant for many processes essential for proper brain function including excitability, myelination and volume regulation, the brain is by far the most commonly affected organ in hyponatremia. The brain lies within the undeformable skull, and therefore a decrease in the extracellular osmolarity, if associated with significant brain volume disturbances, may induce severe anatomical constraints which could lead to mechanical trauma to brain parenchyma and possibly brain herniation [6]. On another hand, rapid correction of hyponatremia can result in severe brain demyelination [7–12] and theoretically, changes in the extracellular concentration of sodium can affect the generation and the propagation of action potential in neurons [13]. Clinically, the neurological manifestations of hyponatremia vary according to several parameters including the rapidity of onset, the severity of hyponatremia and the associated comorbidities. Although the symptoms of hyponatremia have historically been associated with severe hyponatremia (serum sodium of less than 120 mEq/l), for the last two decades, several lines of evidences have suggested that mild hyponatremia which

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was once thought to be asymptomatic carries a significant neurological morbidity [14] and the neurological consequences of the rapid correction of hyponatremia are now well recognised [15, 16].

This chapter will review the mechanism of brain adaptation to hyponatremia and the clinical consequences of hyponatremia and its correction.

General Principles of Brain Volume Regulation

The ability to regulate cell volume is essential for cell survival, and this property has been preserved throughout evolution [17, 18]. The intracellular compartment of the cell is separated from the extracellular compartment by a semi-permeable membrane that is highly permeable to water but not to other solutes. The high permeability of the cell membrane to water is due to the presence of water channels or aquaporins (AQP) [19]. As a consequence of the high membrane permeability to water, both the cell water content and the cell volume are determined by the gradient of osmotically active solutes across the membrane. Cells contain significant amounts of organic molecules, mostly large molecular weight anionic compounds. The cell membrane is impermeable to these intracellular molecules (mostly proteins) and the Gibbs–Donnan equilibrium is achieved to maintain electroneutrality at the expense of a higher concentration of diffusible intracellular cations which occurs to balance the negative charge of the proteins. However, because of that increased concentration of ionic particles inside the cell, there will be an osmotic gradient that would result in an increase water influx inside the cell eventually leading to cell lysis. However, cells do not burst because the Na^+–K^+ ATPase sets a new equilibrium where the outward active transport of sodium counteracts the passive osmotic swelling set by the Donnan equilibrium. A major determinant of the new equilibrium is the establishment of the sodium gradient across the cell membrane which in turn is a main determinant of water movement across the cell. Therefore the cell volume is directly influenced by the extracellular sodium concentration (see [20, 21] for comprehensive review).

In the context of CNS pathology, the regulation of cell volume carries an utmost importance since the CNS is located within the skull which is a rigid structure and an increase in the cell volume will translate into an increase in the volume of the whole brain which may induce fatal brain herniation. After hypoosmotic stimulation, cell swelling that is proportionate to the magnitude of the reduction in the osmolarity of the extracellular space would be expected if the cell acted as a perfect osmometer.

Adaptation of the Brain to Acute and Chronic Hyponatremia

Although generally considered to be distinct, the mechanisms of brain adaptation to acute and chronic hyponatremia can be viewed as a part of the same physiological continuum. Acute hyponatremia is defined as hyponatremia of less than 24–48 h of

duration. Although this definition has very little pathophysiological basis, it has generally been accepted by most clinicians.

During the first hours of hyponatremia (within 30 min), at the CNS level, the rapid decrease in the plasma sodium is followed by an attempt to counterbalance water entry inside the cells. A decrease in the chloride space (extracellular volume) and a quick loss of intracellular electrolytes (Na^+, K^+ and Cl^-) are among the first changes seen after acute dilutional hyponatremia [22]. The mechanisms of intracellular ion depletion, if they were perfect would completely prevent the development of brain oedema. However, both in experimental studies and in clinical practice, acute hyponatremia, if severe enough, will produce symptoms which correlate with brain swelling. There are two main factors that account for the development of brain oedema and symptoms in acute hyponatremia: First, if the rate of brain loss of electrolytes is slower than the rate of sodium decrease, water entry into the brain will invariably occur. Although the mechanisms of brain electrolyte loss are exhausted after 3 h, an animal study showed that after hyperacute hyponatremia (decrease of serum sodium within 2 h from 139 to 119 mEq/l) 89 % of the rabbits died after severe convulsions and histopathological analysis showed significant brain oedema [23]. Interestingly, the tolerance to acute hyponatremia seems to vary depending on species as such a high mortality after acute severe hyponatremia is seldom seen in rats. In humans, it is not unusual to see severe neurological manifestations after acute hyponatremia even if the level of serum sodium is still above 125–128 mEq/l. Second, the magnitude of hyponatremia play an important role since the total amount of electrolytes that the brain cell can lose to maintain their volume constant is limited. If the decrease in serum sodium is initially slow, allowing almost complete brain adaptation, a second acute injury will result in the same manifestations as in hyperacute injury since the brain adaptation has already been exhausted. This has been shown in an experimental setting where acute chronic hyponatremia in rats resulted in the same mortality as hyperacute hyponatremia [24]. The time and the magnitude of serum sodium decline are usually linked in clinical practice and both the severity and the acuteness of the fall in serum sodium influence the magnitude of brain oedema.

When hypoosmolarity develops at a lower rate, i.e. during a more extended period of time, and if the serum sodium its maintained at values roughly above 110–120 mEq/l or even lower, no brain oedema is seen [25] and the analysis of the brain water content in rats after extended period of hyponatremia reveals no differences in the brain water of hyponatremic animals as compared to normonatremic animals [26, 27] and the same is true for humans [28]. However, it is well known that the mechanisms of rapid brain adaptation by electrolyte extrusion are exhausted after 3 h and the absence of brain oedema despite continuation of hyponatremia (more than 3 h) clearly suggest that other mechanisms take place to prevent water accumulation in the brain. It has been demonstrated that during chronic hyponatremia the brain will also use non-ionic osmotic substances to preserve intracellular brain water content. They are called “organic osmolytes” and the chemical nature of these osmolytes has been very well characterised both in

humans and in animals. Several organic compounds including amino acids, sugars, and polyols serve as organic osmolytes and they have been involved into brain adaptation to chronic hyponatremia [27, 29–33].

In vivo, the depletion of organic osmolytes during chronic hyponatremia has been shown to start as early as 4 h [34] after the induction of hyponatremia and this phenomenon seems to be roughly at its maximum 4 days after the induction of hyponatremia [27]. The main organic osmolytes that are depleted in the brain during hyponatremia are myoinositol, taurine, betaine, glutamate, glutamine and glycerophoshocholine [27, 35]. Interestingly the kinetics of depletion is not uniform for all the osmolytes as some will continue being depleted from the brain as hyponatremia progresses and some will reach a threshold. It is unclear whether or not they are interchangeable and what is the relative importance of each osmolyte in the process; in other words, we do not know if preventing the movement of one of the organic osmolytes will result in adaptation failure or if it will be compensated by an increased extrusion of a different organic osmolyte.

The rate, the magnitude and the geographical distribution of organic osmolyte depletion and their reaccumulation has been hypothesised to be the basis of the neurological effects of hyponatremia and its correction on the brain [36, 37].

Molecular Mechanisms of the Regulation of Brain Adaptation to Hyponatremia

Astrocytic AQP4

The cellular pathways of adaptation to hyponatremia have been extensively studied and it has been shown that AQP4 is a key component in the brain response to hyponatremia. AQP4 is expressed in astrocyte end feet and mediates bidirectional transport of water. It has been shown that the neurological consequences of hyponatremia are alleviated in animal mice deficient of AQP4 [38] and conversely the overexpression of AQP4 in mice results in a increased vulnerability to acute water loading [39].

Volume-Activated Ions Channels

The movement of water through water channels is governed by the osmotic gradient created by several other channels called volume sensitive channels (VSC) There are several members in the family of VSC and their molecular identity remains unclear (for review, see [40]).

Organic Osmolytes Transporters

Several sodium-dependent or -independent organic osmolyte transporters including the transporters for sodium myo-inositol [41], taurine [42, 43] and betaine-GABA have been involved in the movement of organic osmolytes out of the brain cells during hypoosmolarity but it is unclear whether or not it is their activity that is regulated or if the regulation is mainly transcriptional.

Neurological Complications of Hyponatremia in Humans: Hyponatremic Encephalopathy

The clinical syndrome resulting from the effect of hyponatremia on the brain is termed hyponatremic encephalopathy (HNE). The clinical spectrum of HNE is very broad and reflects the extraordinary complexity of brain volume regulation. Although it had been generally held that HNE is clinically significant only in the setting of severe hyponatremia either acute or chronic, recent evidence shows that even patients with moderate hyponatremia can present with signs of HNE not directly related to brain swelling [44].

Risk Factors for Hyponatremic Encephalopathy

Severity and Acuteness of Onset of Hyponatremia

Experimental studies have shown that the increase in the brain volume associated with hyponatremia occurs only in the setting of acute hyponatremia when the mechanism of brain depletion of organic osmolytes are not yet fully active and therefore cannot prevent the abrupt increase in the cell volume caused by a low extracellular sodium. On the contrary, after 48 h of hyponatremia, there are minimal changes in the brain volume and in rats made hyponatremic for 3 weeks, the total brain water content was unchanged as compared to rats with normonatremia [26, 27] and this is similar in human subjects [28]. This notion is supported by the observation that most patients with the most dramatic manifestations of HNE actually have acute and severe hyponatremia, for example, as seen in the setting of perioperative care with the use of hypotonic fluids.

Gender and Age

Gender and age have also been associated with the manifestations of hyponatremia [45, 46].

The high prevalence of HNE in children has been explained by the large brain to intracranial ratio in children [45]. The brain reaches its adult size at 6 years old which is much earlier than the non-distensible skull which reaches its maximal volume at 16 years of age. Therefore, any increase in the size of the brain in children, resulting from an increase in the intracellular brain cell volume as seen in acute hyponatremia will have to occur within a smaller intracranial volume at the expense of brain parenchyma compression and possible hernia.

The high mortality and morbidity in children from hyponatremia has been acknowledged by several clinical studies [47–51]. Other factors explaining the high incidence of hyponatremic-related death in young patients is the widespread use of hypotonic fluids for volume resuscitation [48].

Several studies from the same group have suggested that the female gender is another risk factor for HNE and surprisingly the predisposition for HNE has been reported in both pre menopausal and postmenopausal females [6, 45, 46, 52–54]. However, this notion has not been confirmed in an extensive review of more than 250,000 cases [55], so that the female predisposition to HNE remains uncertain. Likewise, experimental data are difficult to reconcile because, although in vitro female sex hormone were shown to impact volume regulation in astrocytes [56], the in vivo studies did not support a significant role of female sex hormone in brain adaptation to hyponatremia and its consequences. Further, hyponatremic rats either male or female have been shown to have the same pattern of brain adaptation to hypotonicity [26, 34]. The extensive use of hypotonic fluid during gynaecological procedures might partly explain why females seemed to be at higher risk of HNE.

Hypoxia

The concurrent occurrence of hypoxemia can impede the mechanisms of brain adaptation to hyponatremia and may precipitate or worsen HNE. There is now clear experimental and clinical evidence that hypoxemia is a very poor prognostic factor in hyponatremia. Ayus showed that association of hypoxia and hyponatremia is a major determinant of neurological damage [53]. These studies were replicated in an animal model showing more brain damage in rats and rabbits with hyponatremia and concomitant hypoxia [57, 58]. Although the levels of hypoxia reached in the experimental studies were very low and rarely encountered in clinical practice, the association of hyponatremia and mild or moderate hypoxia in the intensive care setting is common and might explain the worse prognosis in this subgroup of patients.

Diagnostic of Hyponatremic Encephalopathy

The diagnosis of HNE relies on clinical, biological data and imaging. The findings will vary according to the severity of the hyponatremia, the underlying conditions and the age of the subject as discussed above.

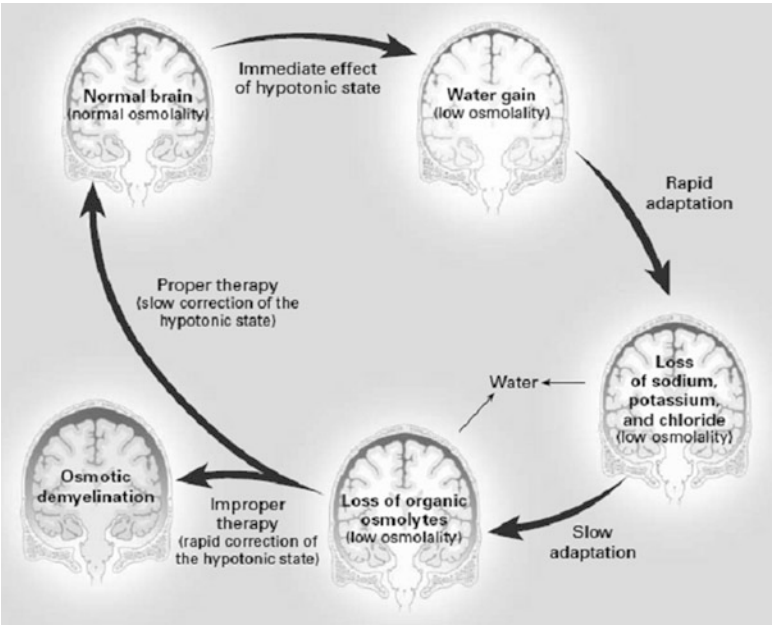

Fig. 5.1 Effects of hyponatremia and its correction on the brain. Physiopathology of brain complications of hyponatremia and its correction. Adapted from Adrogué and Madias [1], with permission from the Massachusetts Medical Society

Clinical Manifestations of Hyponatremic Encephalopathy

Acute Hyponatremia

It is generally believed that the neurological symptoms of acute hyponatremia are related to the degree of brain oedema and the development of brain oedema is strongly associated with the ability of brain cells to extrude osmolytes in order to maintain their volume (Fig. 5.1). The cut-off of 48 h has been clinically accepted to differentiate acute from chronic hyponatremia. It is understood that the electrolyte contribution to volume regulation is exhausted by 3 h and the non-electrolyte contribution to the volume regulation has been shown to start as early as 4 h after the induction of hyponatremia [34] with significant differences in the brain content of organic osmolytes being observed at 24 h [32] and thereafter [27, 35]. For these reasons, hyponatremia of more than 24 h duration is generally considered "chronic" since it is associated with significant compensation and a decreased likelihood of brain oedema.

Some have reported that acute and severe hyponatremia is associated with a high mortality reaching 50 % in some reports, along with significant morbidity [6, 59]. The most commonly reported symptoms include severe nausea from intracranial hypertension, seizures and coma (Fig. 5.2 and Table 5.1). Some patients will

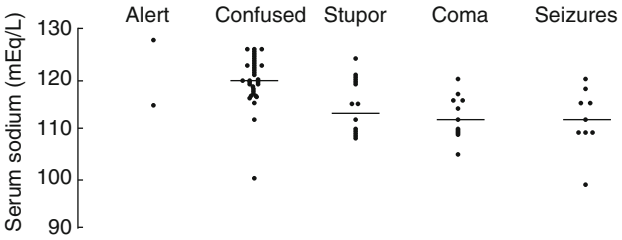

Fig. 5.2 Symptoms of acute hyponatremia. Neurological symptoms of acute hyponatremia. There is a considerable overlab in the neurological symptoms and some of them can be seen with a serum sodium around 125–130 mEq/l. Adapted from Arieff et al. [23], with permission

Table 5.1 Manifestations of hyponatremia

Acute (<48 h)	Chronic (>48 h)
Nausea and vomiting	Fatigue
Headaches	Confusion
Seizures	Somnolence
Coma	Gait deficit
Respiratory arrest	Attention deficit
Death	Falls

experience explosive symptoms like seizures followed 20 min later by respiratory arrest [23, 60]. These manifestations can occur independently, simultaneously or can overlap in some patients.

The occurrence of respiratory arrest in the setting of severe hyponatremia has been well documented [60, 61] and seems to be secondary to non-cardiogenic pulmonary oedema or central hypoxia from brain oedema. That situation creates a vicious cycle of perpetuated brain damage which leads to devastating neurological consequences. Although generally most of these manifestations will not occur until the serum sodium is below 120 mEq/l, they may occur at higher values [62].

Mild and moderate acute hyponatremia has been regarded as pauci symptomatic or asymptomatic in terms of neurological manifestations. However, recent literature from sports medicine suggests that people who developed acute hyponatremia with a serum sodium level of >120 mEq/l can experience nausea, lethargy, acute confusion and vomiting which are reversed after treatment of hyponatremia [63].

Chronic Hyponatremia

The symptoms of severe chronic hyponatremia are usually milder than severe acute hyponatremia reflecting the brain adaptative changes that occurred in order to limit brain swelling. In a study involving elderly patients with hyponatremia, it was shown that elderly individuals with mild and moderate hyponatremia (128 ± 2 mEq/l) have profound impairments in gait and attention compared to patients with normonatremia [44] (Fig. 5.3). This resulted in an increased risk of falls and

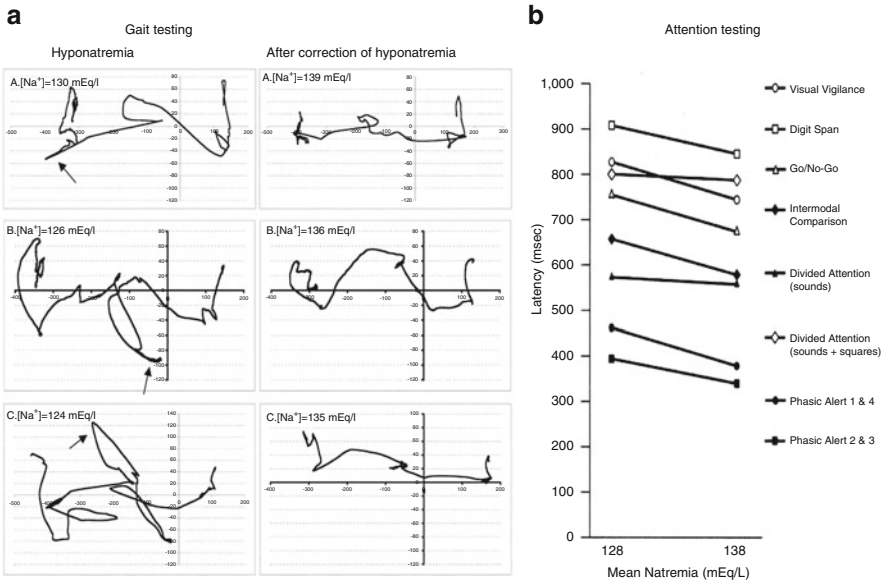

Fig. 5.3 Mild hyponatremia and gait imbalances. Gait is impaired in mild hyponatremia and correction of hyponatremia can normalise the gait (**a**). (Adapted from Renneboog et al. [44] with permission from Elsevier.) Attention is also disturbed in mild hyponatremia with normalisation upon correction of serum sodium (**b**). (Adapted from Decaux [14] with permission from Elsevier)

bone fractures [64–66]. Although some recent evidence has suggested that hyponatremia affects bone structure [67, 68], HNE itself is probably an important factor in the risk of bone fractures in elderly individuals [66, 69]. The gait and attention deficits observed in mild hyponatremia were reversible upon treatment of hyponatremia, suggesting that hyponatremia itself was the main culprit. These disturbances have now been described with a serum sodium as high as 132–134 mEq/l and interestingly they seem to be more prevalent and more severe in older patients as compare to young individuals [70]. Other symptoms associated with chronic hyponatremia include confusion and somnolence despite absence of cerebral oedema [28]. However, even in chronic hyponatremia, the most devastating symptoms such as seizures occur mostly because of brain swelling [23]. In a small study of patients presenting with severe hyponatremia, those who later went on and developed seizures had a significant change in the size of their intracerebral ventricule after the correction of hyponatremia suggesting significant brain oedema occurred in the hyponatremic phase. In contrast, patients who had no seizures had no changes in the volume of their ventricle after the treatment [71]. It should be mentioned that it has not yet been clearly established that patients who present with no evidence of brain oedema will suffer from seizures. Decreased conduction velocities have been reported in severe hyponatremia and it is also likely that during hyponatremia the threshold for seizures will decrease [13].

Brain Imaging in Hyponatremic Encephalopathy

In severe acute hyponatremia, when the mechanisms of brain adaptation to hypoosmolarity are overwhelmed either by the rapidity of the onset of hyponatremia or its depth, radiological signs of brain oedema can be seen in brain CT scan or MRI. These include effacement of sulci, effacement of quadrigeminal cistern, and generalised brain swelling along with possibly early signs of brain herniation.

In patients with chronic hyponatremia, brain scans will generally appear normal which corroborates the absence of brain oedema [28]. Interestingly, in face of hyponatremia of uncertain duration, some have advocated the use of brain imaging for detection of brain oedema to guide the rate of correction [72].

Pathological Findings in Hyponatremic Encephalopathy

Few studies have addressed the pathological findings of chronic HNE in humans or animals. The rare studies that were done are biased by the fact that only gross morphological analyses were done; it is unclear whether or not chronic HNE affects the ultra-structure of brain cells. Analysis of the brain of asymptomatic chronic hyponatremic rats is grossly similar to the brain of normonatremic animals. The blood brain barrier (BBB), oligodendrocytes and neurons appear to be preserved in chronic hyponatremia [73, 74]. Although previous literature has suggested that HNE was the cause of lesions of demyelination, follow up studies have clearly demonstrated that osmotic demyelination is not a pathological feature of chronic hyponatremia.

In acute and severe hyponatremia, morphological evidence of diffuse cerebral oedema is present, with or without herniation. Infarction of the anterior and posterior pituitary lobe, neuronal ischemia and medullary infarction have also been described [75].

Treatment and Prognosis of Hyponatremic Encephalopathy

Symptomatic HNE is a medical emergency. Severe untreated HNE has a very bad prognosis and many patients will die from consequences of brain oedema and herniation [52, 54, 76, 77]. Patients presenting with the symptoms of HNE should be treated with hypertonic saline to prevent further neurological damage [77, 78]. The modalities of treatment are discussed in another chapter but the general consensus is that the treatment should take into consideration the risk of delayed neurological decline associated with osmotic demyelination.

Neurologic Consequences of the Rapid Correction of Hyponatremia: Osmotic Demyelinaton Syndrome (ODS)

The detrimental effects of water intoxication were known long before measurement of serum sodium became widely used and it was also acknowledged that the neurological manifestation of water overdose could be prevented by the administration of hypertonic saline [79–83]. However, from the late 1970s to the early 1980s, emerging studies suggested a link between the rapid correction of hyponatremia and demyelinated brain regions in malnourished and alcoholic patients [8, 10, 11, 84, 85]. The experimental counterpart of central pontine myelinolysis (CPM) after correction of hyponatremia was first described in 1981, and since then, validation of hyponatremia correction as a risk factor for CPM was provided by numerous experimental studies [7–9, 11, 86]. Clinically, many reports have established that the rapid correction of chronic hyponatremia is the principal determinant for osmotic demyelination syndrome (ODS) in patients in whom such interventions was undertaken [12, 87–89].

Risk Factors for Osmotic Demyelination

Small case studies have helped to characterise the risk factors for CPM and extrapontine myelinolysis (EPM) [90–92]. Surprisingly, although the rapid correction of hyponatremia appears to be an important risk factor, only roughly one-third of the patients with pathologically or radiologically diagnosed CPM had an episode with the rapid correction of hyponatremia [93, 94] suggesting that ODS (which is CPM or EPM occurring specifically after the correction of hyponatremia) represents only a small percentage of cases of CPM/EPM. The term ODS should be reserved to describe the constellation of CPM/EPM on imaging or pathology along with biochemical evidence of osmotic imbalance.

Alcoholism and solid organ transplant, especially liver transplants with the use of cyclosporine, also have a high risk of demyelination [95]. These associations are present independently of hyponatremia but have not yet been investigated in experimental studies, and it is unclear whether central and extra pontine myelinolysis (CPM or EPM) in liver failure or alcoholism without hyponatremia share the same physiopathology as ODS.

Although in the 1980–1990s the modalities of the treatment of severe hyponatremia were controversial [96–99], there are now several guidelines regarding the rate of correction of hyponatremia in patients with chronic severe hyponatremia [16, 100–104] (and covered in this book). Initial retrospective studies established that patients who had a magnitude of correction of more than 12 mEq/l/24 h, which corresponds to a rate of correction of more than 0.5 mEq/l/h/24 h [88, 105], have the highest risk of ODS. However, animal studies showed that not only the rate of correction but also the initial absolute changes in the serum sodium

value before and after the treatment are important in the likelihood of neurological lesions due to ODS [106–108]. The duration of hyponatremia also carries a significant weight. ODS has been shown experimentally to be more frequent in animals with an hyponatremia lasting more than 2 days [109] and in clinical practice successful rapid correction of acute hyponatremia has been achieved with no demyelination. Hypokalemia appears to be another strong risk factor for osmotic demyelination but this has not yet been investigated by experimental studies [94, 110]. Also, age, alcoholism and malnutrition have been associated with osmotic demyelination after the rapid correction of chronic hyponatremia in the clinical setting but the extent of these relationships is difficult to assess because these associations were derived mostly from retrospective studies, and to date, no experimental studies have explored the importance of these factors.

Diagnosis of Osmotic Demyelination

The diagnosis of osmotic demyelination requires a high index of suspicion. Although the experimental studies in rats have shown that signs and symptoms of ODS can occur as early as 12 h after rapid correction, the clinical picture in humans is usually delayed by 2–3 days after the correction of hyponatremia and a biphasic course is the most frequent pattern. As patients with chronic and severe hyponatremia might already have some neurological symptoms (confusion, somnolence, etc.), the correction of hyponatremia will result in an apparent neurological improvement which heralds further neurological deterioration as the ODS symptoms start. Other forms of clinical presentation have been described like a monophasic pattern in patients with a very important magnitude of correction where the stupor from correction of hyponatremia overlaps with the altered consciousness induced by severe hyponatremia itself [89]. Some have also described a delayed course of subtle manifestations occurring very long after correction of serum sodium [111].

The early diagnosis relies on careful clinical exam in conjunction with laboratory analysis to identify any raise in the serum sodium. Radiological features are typical but appear late in the course.

Clinical Symptoms of ODS

The clinical symptoms of ODS vary widely, probably reflecting the diversity of the areas of brain involved. Both motor and sensory neurological deficits have been described in the setting of ODS (Table 5.2), these include bulbar symptoms such as occulomotor abnormalities, dysphagia, diplopia or extrapyramidal features like tremor and limb dissymmetry. The most dramatic symptoms are coma, quadriparesis and locked-in state [12, 89, 105, 112, 113]. Recent reports have proven that various psychiatric symptoms can also occur during the clinical course

Table 5.2 Neurological manifestation of ODS

Motor and sensory	Psychiatric and neuropsychologic
Seizures and coma	Dementia
Dysarthria, anarthria and dysphagia	Altered
Dysmetria, ataxia and dystonia	Depression
Akineto-rigid syndrome	Concentration
Tremor	Altered memory
Paraplegia and locked in syndrome	Catatonia
Ocular movement disorders	
Cortical blindness	

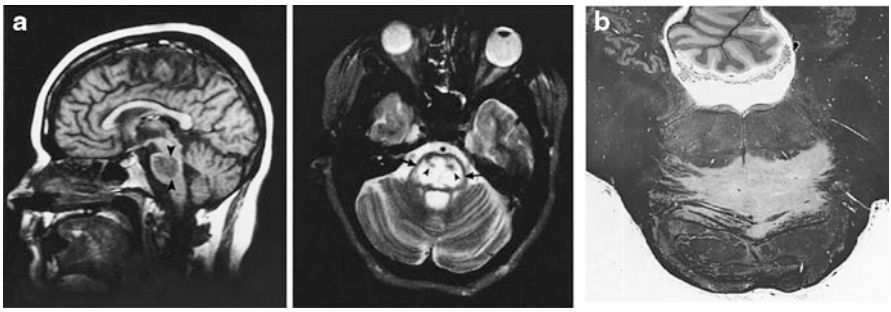

Fig. 5.4 Radiological and pathological features of osmotic demyelination syndrome. (**a**) Radiological features of osmotic demyelination syndrome. A well-circumscribed lesion is seen at the base of the pons in panel **a**. Panel **b** shows loss of myelin at the base of the pons (luxol fast blue was used to stain myelin). Adapted from Haart B, Eaton RP. NEJM. (1995);333:1259, with permission form the Massachusetts Medical Society (**a**) and Martin RJ. J Neurol Neurosurg Psychiatry. (2004):75 with permission from BMJ Publishing Group Ltd. (**b**)

of ODS. The reported psychiatric features include paranoia, restlessness, apathy, and changes in mood state [114–118]. Neuropsychological manifestation including dementia has also been reported [119].

Radiological Features of Osmotic Demyelination

ODS is best diagnosed with MRI and the radiological features include hyperdense lesions on T2-weighted images and hypodense non-enhancing lesions on T1-weighted images (Fig. 5.4a and Table 5.3). CT Scan has been used for the diagnosis of ODS but CT usually fails to shows the initial changes [115, 120–122]. Delayed CT usually shows low attenuation in the demyelinative regions [121]. Some radiological reports have suggested no correlation between the volume of the MRI lesions and the symptoms [123, 124] and a few studies have documented resolution of the salient imaging findings after clinical recovery which illustrate some potential of myelin regeneration [125, 126].

Table 5.3 Radiological and pathological features of ODS

	Early lesions	Late lesions
Pathology	BBB breakdown	BBB breakdown
	Astrocyte death	Severe peripheral gliosis
	Mild gliosis	Myelin loss
	Little or no myelin loss	Dense microglial infiltrate
	No microglial infiltration	
Radiology CT	Normal CT	Hypodense lesions
MRI	Hyperdense T2 MRI lesions	Hyperdense T2 MRI lesions
	Hypodense T1 MRI lesions	Hypodense T1 MRI lesions

Pathological Features of Osmotic Demyelination

The salient lesion in ODS is a demyelination of the affected part of the brain which is obvious after staining for luxol fast blue (Fig. 5.4b). Immunohistostaining for myelin basic protein will reveal areas of loss of myelin which are sharply demarcated from the normal brain [86, 127]. Demyelination is usually symmetric and affects several brain regions including the subcortical region, the basal ganglia, the pons and sometimes the cerebellum. Demyelination is accompanied by oligodendrocyte loss and a dense microglial infiltrate within the lesion [86, 127].

Staining for astrocytes will reveal their loss in demyelinative foci along with a strong glial reaction at the borders of the lesions (Fig. 5.5). So far, no involvement of peripheral-derived immune cell has been reported. Early findings include a breakdown of the BBB and astrocyte loss [73, 128]. Neuronal preservation has been described in most pathological instances of ODS but a single report has suggested that axonal damage might also occur [129].

Pathophysiology of Osmotic Demyelination

Despite significant amount of work during the past few decades on the topic, the pathophysiology of ODS is still unclear. The opening of the BBB and microglial activation have been long thought to be the cardinal features of the disease [130]. Indeed, it was believed that the osmotic stress will induce the opening of the BBB which will expose the brain to diverse myelinolytic substances and activate microglia leading to further neurological damage [130–132]. However, we recently showed that astrocytes are the earliest target in ODS as severe astrocytic apoptosis is observed as early as 12 h after the correction of hyponatremia when there is no morphologic evidence of myelin loss [73]. Furthermore, we and others have demonstrated that opening of the BBB does not necessarily result in myelin loss and likewise, a closed BBB does not completely protect against osmotic demyelination [74, 133, 134]. Functional astrocytes are required to maintain BBB permeability [135] and we observed that BBB leakage occurred at the same region and

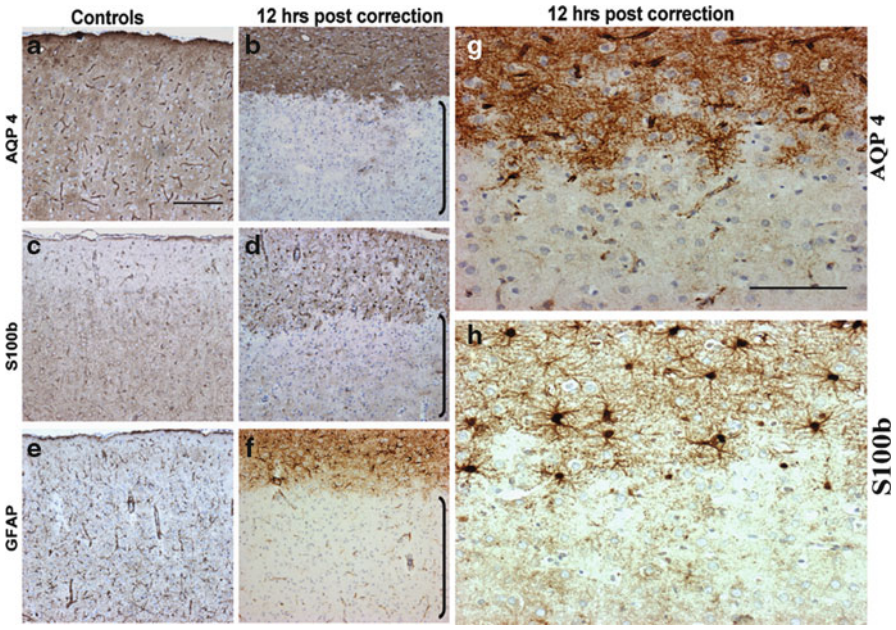

Fig. 5.5 Loss of astrocyte in experimental osmotic demyelination syndrome. Loss of astrocytes is evident as early as 12 h after the correction of hyponatremia in rat brains. A glial reaction is seen in the periphery of the main lesion. (astrocytes were stained by anti AQP4, anti GFAP and anti S100B). Adapted from Gankam Kengne [73] with permission

time as astrocyte death hinting that BBB leakage might actually be secondary to astrocytic damage.

As for the role of activated microglia, it is now clear that they appear at the site of the lesions long after astrocyte death and concomitant with the first evidence of demyelination [73, 134]. Several treatments which act upon microglial activation have shown variable efficacy in ODS and microglia itself undergo significant morphologic and phenotypic changes, accompanied by changes in their cytokine profile (initially inflammatory and then protective). This all suggests that they might play a dual role at the different times of the disease. Initially they might exacerbate the inflammatory reaction induced by astrocytic death but later they might scavenge the myelin debris and prevent the extension of the demyelination.

Prevention and Treatment of Osmotic Demyelination

Treatment of osmotic demyelination relies on rapid identification of the high-risk patient and careful correction of hyponatremia. Although several reports have pointed that even 'slow' correction of hyponatremia can result in demyelinative brain lesions [112, 136–138], most cases of ODS associated with sodium correction

occur when the correction exceeds 10 mEq/l/24 h. Therefore, it is of foremost importance to limit the correction of serum sodium in chronic hyponatremia within that range or lower during the first 24 h. Several strategies can be applied to obtain such limits, the most important being frequent (every 2–4 h) electrolyte monitoring.

There is now convincing clinical and experimental evidence suggesting that after rapid correction, relowering of serum sodium can prevent development of neurological symptoms [74, 139, 140]. To be fully effective, relowering has to be started within the first 24 h and the goal should be to maintain the rate of correction to less than 6 mEq/l/24 h.

Dexamethasone has been used for the treatment of ODS but experimental data have suggested that dexamethasone has little or no efficacy when given 6 h after the correction has been achieved [74].

Experimental data have suggested that minocycline, a second generation tetracycline, can be effective and administration of that drug in animals resulted in decreased permeability of the BBB along with reduced microglial activation and significant decrease in the neurological impairment and pathological lesions [133, 141]. The usefulness of minocycline in humans has not yet been investigated.

Other experimental data have also suggested that correction of hyponatremia with urea as opposed to hypertonic saline could result in significant protection against osmotic demyelination [142–145]. Indeed, urea can induce water diuresis and has been used to correct hypervolemic and euvolemic hyponatremia with excellent results. When compared to hypertonic saline or water diuresis in animals, those animals who received urea were less likely to manifest neurological complications than animals in the other two groups [143, 144, 146]. There are now consistent data suggesting that the adaptation pathways to an increase in the tonicity of the cell are largely different after exposure to urea or hypertonic saline [147, 148] and it is very likely these different intracellular responses after correction of hyponatremia with urea versus hypertonic saline might impact the likelihood of developing subsequent demyelination. Conflicting reports exist in ODS in uremic patients during dialysis sessions [149–151] and a recent review suggested that ODS can indeed occur in uremic patients after dialysis sessions [152] although the causal relationship between the rise in sodium and the lesions could not be established rigorously as neurological complications of uremia and dialysis can radiologically and clinically present like ODS. Whether or not the incidence of ODS in uremic patients is lower than in non-uremic patients remains to be investigated but at this point in time, rapid correction of serum sodium by dialysis is not recommended.

The topography of the lesion of osmotic demyelination is very similar to the kinetic of reaccumulation of organic osmolytes with the regions with the slowest rate of re-accumulation being the most affected [29, 36]. In an experimental study, myoinoistol, one of the major organic osmolyte depleted in chronic hyponatremia has been used to prevent neurological complications of rapid correction of hyponatremia in rats [37]. At this point, it remains unclear if myoionositol can be used in humans and we don't know if other organic osmolytes such as taurine or betaine can be used to prevent ODS.

Prognosis of Osmotic Demyelination

The first reports of osmotic demyelination suggested a grim prognosis and many patients either died or were left in a persistent vegetative state [84, 153, 154]. The prognosis of ODS has therefore been considered as very poor. However, recent reports have suggested that the prognosis of ODS is actually better than previously thought, with roughly half of the affected patient surviving with minimal neurological sequellae [90, 91, 155]. One study reported that 11 out of 24 patients with radiologically and clinically proven demyelination had a favourable outcome with as many as 7 of them returning to baseline neurological function [91]. Another study reported a favourable Rankin score in 18 out of 36 patients analysed [155]. In these studies, the level of hyponatremia before the correction and chronic alcoholism were found to be associated with a worse outcome. It should be mentioned that these studies dealt with cases of radiologically and clinically proven ODS and it is reasonable to believe that some case of mild ODS were not included because the clinical manifestations did not prompt thorough neurological or radiological examination.

Conclusion

Despite the elaborate mechanisms of adaptation to hypotonicity induced by hyponatremia, the brain anatomical structure and constraints imposed by the surrounding skull and the iatrogenic interventions determine cerebral vulnerability to hyponatremia and its treatment. The brain is the main organ affected by hyponatremia and the neurological manifestations extends from fatal brain oedema to gait and attention deficit. While most of the neurological manifestations of acute severe hyponatremia can be explained by brain oedema, the physiological mechanisms involved in the changes induced by chronic hyponatremia where no brain oedema is seen, remain enigmatic. Substantial amount of work is required to better characterise the physiopathology of these symptoms.

On the other hand, perhaps the most intriguing pathological response of the brain to sudden osmotic stress is the peculiar demyelination found after rapid correction of hyponatremia. Both the severity of hyponatremia and inappropriate correction of hyponatremia are associated with a poorer prognosis. Rapid recognition of HNE symptoms and caution during correction of chronic hyponatremia can help the clinician to prevent irreversible brain damage.

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Chapter 6
Hyponatremia Induced by Drugs

George Liamis and Moses Elisaf

Medications make up one of the most frequent causes of hyponatremia. They may induce hyponatremia by affecting either the sodium and water homeostasis (diuretics) or the water homeostasis due to the syndrome of inappropriate secretion of antidiuretic hormone (SIADH) [1]. There are three possible ways drugs can affect water homeostasis: they can increase ADH secretion centrally, potentiate the effect of endogenous ADH at the renal medulla, and reset the osmostat, thus lowering the threshold for ADH secretion. SIADH can also be produced by exogenous ADH or oxytocin administration. Hyponatremia-related to drug treatment can be caused by dozens, perhaps hundreds, of medications. Table 6.1 lists the drugs associated with hyponatremia.

Diuretics

Diuretics are among the most common causes of hyponatremia, especially in outpatients [2, 3]. Virtually, all cases of diuretic-induced hyponatremia are caused by thiazide or thiazide-like agents [4–11]. Loop diuretics are occasionally associated with hyponatremia because they impair both the renal concentrating and diluting mechanisms [4, 8]. Loop diuretics reduce the osmolarity of the medullary interstitium by inhibiting NaCl reabsorption in the thick ascending limb of the loop of Henle. On the contrary, thiazide diuretics acting solely in the distal tubules do not interfere with urinary concentration and the ability of antidiuretic hormone (ADH) to promote water retention, which is the critical point for the development of hyponatremia.

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Table 6.1 Causes of drug-induced hyponatremia according to probable underlying mechanisms

A. Drugs affecting sodium and water homeostasis
- *i.* Diuretics
  - – Thiazides
  - – Indapamide
  - – Amiloride
  - – Loop diuretics
- *ii.* Theophylline
- *iii.* Co-trimoxazole

B. Drugs affecting water homeostasis
1. Increased hypothalamic production of ADH
   - *i. Antidepressants*
     - – Tricyclic antidepressants (amitryptiline, protriptyline, desipramine)
     - – Selective serotonin reuptake inhibitors (SSRIs)
     - – Monoamine oxidase inhibitors
   - *ii. Antipsychotic drugs*
     - – Phenothiazines (thioridazine, trifluoperazine)
     - – Butyrophenones (haloperidol)
   - *iii. Anticonvulsants drugs*
     - – Carbamazepine, oxcarbazepine, sodium valproate, levetiracetam
   - *iv. Antineoplastic and immunomodulating agents*
     - – Vinca alkaloids (vincristine, vinblastine)
     - – Platinum compounds (cisplatin, carboplatin)
     - – Alkylating agents (intravenous cyclophosphamide, melphalan, ifosfamide)
     - – Miscellaneous (methotrexate, interferon α and γ, levamisole, pentostatin, monoclonal antibodies, tacrolimus)
   - *v. Other*
     - – Opioids
     - – Amphetamines
     - – Angiotensin-converting enzyme inhibitors
     - – Antiarrhythmics (amiodarone, lorcainide, propafenone)
     - – Antibiotics (ciprofloxacin, rifabutin, vidarabine)
     - – Proton pump inhibitors
     - – Theophylline
2. Potentiation of ADH effect
   - *i. Anti-epileptic drugs*
     - – Carbamazepine, lamotrigine
   - *ii. Antidiabetic drugs*
     - – Chlorpropamide, tolbutamide, insulin
   - *iii. Anticancer agents*
     - – Alkylating agents (intravenous cyclophosphamide)
   - *iv. Nonsteroidal anti-inflammatory drugs*
3. Reset osmostat
   - *i. Antidepressants*
     - – Venlafaxine
   - *ii. Anti-epileptic drugs*
     - – Carbamazepine

(continued)

Table 6.1 (continued)

4. Exogenous administration of ADH
– Oxytocin
– Vasopressin
C. Dilutional or translocational hyponatremia
i. Mannitol
ii. Immune globulin (intravenously)
D. Pseudohyponatremia
i. Immune globulin (intravenously)

It is worth mentioning that loop diuretics causing hypotonic renal losses are successfully used in the treatment of euvolemic and hypervolemic hyponatremia. Moreover, if the loop diuretics-induced renal water losses are replaced insufficiently, hypernatremia rather than hyponatremia may ensue [12]. Interestingly, in patients with previous thiazide-associated hyponatremia who clearly require a diuretic, furosemide may be administered without risk for recurrent hyponatremia [13]. Hyponatremia is also a complication of indapamide administration [14]. It has been reported that indapamide leads to less hyponatremia than hydrochlorothiazide in hypertensive patient [15]. However, even the low dose of the drug (indapamide sustained release 1.5 mg daily) can induce severe hyponatremia (serum sodium $<$ 125 mmol/L) [16].

Moreover, hyponatremia has been described when amiloride or spironolactone were combined with thiazide diuretics. The association can be explained physiologically, because these drugs inhibit sodium reabsorption in the renal collecting duct, causing salt wasting [17, 18]. Effects of thiazides are mainly on the distal tubule; therefore, the combination compounds the urinary loss of sodium.

Interestingly, despite numerous studies, the underlying pathophysiological mechanisms of diuretic-induced hyponatremia remain unclear. The most important implicated mechanisms of diuretic-related hyponatremia are as follows: (1) excess renal loss of effective solutes ($K^+ + Na^+$) compared with water losses resulting both from diuretic-induced electrolytes losses and ADH-induced water retention, (2) appropriate stimulation of the ADH secretion because of diuretic-induced volume depletion, (3) the coexistent hypokalemia that leads to a transcellular cation exchange in which K^+ leaves the cells while Na^+ moves into the cells, (4) the direct inhibition of urinary dilution by diminishing NaCl reabsorption in the renal tubules, (5) stimulation of thirst, (6) magnesium depletion, and (7) excessive ADH secretion [4–11, 19].

These various mechanisms implicated in diuretic-induced hyponatremia have both clinical and laboratory reflection. In fact, it appears that there are two groups of patients with diuretic-related hyponatremia, one that is consistent with extracellular volume depletion and another that simulates the syndrome of antidiuretic hormone secretion (SIADH). Serum uric acid level ($<$4 mg/dL and $>$4 mg/dL, respectively) has been considered as a useful index in discriminating between these two pathophysiological constructs [3].

Of note, the incidence of thiazide-induced hyponatremia has not been well studied. Indeed, in patients with thiazide-associated hyponatremia, not infrequently, multiple potential risk factors for hyponatremia are present obfuscating the contribution of thiazides [20, 21]. Consequently, the incidence of thiazide-associated hyponatremia ranged widely depending on the population at risk, differences in diuretic choice, and the definition of hyponatremia used in the various studies. For example, in a recent retrospective cohort study 66 (30 %) out of 220 hypertensive patients exposed to ongoing thiazide therapy exhibited hyponatremia (defined as serum sodium concentration $\leq$130 mmol/L) [22]. However, in the Systolic Hypertension in the Elderly Program (SHEP) study, hyponatremia (serum sodium $<$130 mEq/L) was observed in 4.1 % of patients treated with chlorthalidone vs. 1.3 % in the control group [23]. The thiazide-induced hyponatremia typically begins soon after the onset of thiazide therapy, though there is a wide variation in the timing of presentation [8, 24]. It appears that the use of thiazides is associated with a dose-dependent reduction in serum sodium levels. In fact, it has been reported that in patients with thiazide-related hyponatremia an average daily hydrochlorothiazide dose of 35 mg was required to induce hyponatremia, with 44 % of patients receiving $\geq$50 mg [25]. On the other hand, in a study of hypertensive subjects who exhibited diuretic-induced hyponatremia, only 10 % of them were on low dose hydrochlorothiazide (12.5 mg/day) [24].

Moreover, older age, female gender, low body mass, intercurrent illnesses or conditions that stimulate water intake or ADH release, low salt intake, and concurrent use of other medications that impair water excretion (e.g., nonsteroidal anti-inflammatory drugs, selective serotonin reuptake inhibitors [SSRIs]) represent risk factors of thiazide-induced hyponatremia [4, 7, 10, 26–28]. Finally, hypokalemia has also been recognized as an independent risk factor for the development of diuretic-induced hyponatremia [2]. This may be of great importance not only because hypokalemia is frequently observed in hyponatremic patients due to diuretics but also because there is some evidence in animals and in man that hypokalemia when present in the hyponatremic state could predispose to the development of demyelination during correction of the hyponatremia [29–32].

A history of diuretic use and the restoration of normal serum sodium levels after discontinuing the offending agent comprise the cornerstone for the accurate diagnosis of diuretic-induced hyponatremia. However, 1–2 weeks may be required for the achievement of normonatremia and the full recovery of diluting ability after drug withdrawal. Consequently, in patients with diuretic-induced hyponatremia and an SIADH-like profile, unless there is strong evidence to suggest an underlying cause for SIADH, a comprehensive diagnostic evaluation should be postponed for 2–3 weeks. However, taking into account that thiazides may aggravate the hyponatremia induced by SIADH, this evaluation should be undertaken if even mild hyponatremia persists after this diagnostic waiting period.

Psychotropic Agents

A wide array of psychotropic medications is associated with hyponatremia, including antidepressants (tricyclics, SSRIs, and monoamine oxidase inhibitors), benzodiazepines, and antipsychotic drugs (phenothiazines, butyrophenones) [28, 33–43]. The mechanism by which these drugs exert their effects on serum sodium levels is thought to be the development of SIADH. Furthermore, hyponatremia caused by a reset osmostat syndrome variant of SIADH has been described after treatment with venlafaxine, a serotonin and norepinephrine reuptake inhibitor [44].

However, a precise estimation of the contribution of the psychotropic drugs in the development of hyponatremia in psychiatric patients is often difficult to demonstrate. Indeed, among the most frequently implicated causes of hyponatremia in this population are the underlying psychosis per se [45] and the compulsive water drinking. Psychogenic polydipsia is a common symptom in patients with a variety of psychiatric disorders, including psychotic depression and manicdepressive psychosis, but it is especially prevalent in patients with schizophrenia [46–48]. In addition to the underlying psychosis, the sensation of a dry mouth caused by psychotropic drugs (especially phenothiazines) leads to increased water intake [41]. Thus, causality between psychotropic agents and hyponatremia was shown more convincingly with antidepressants and mainly with SSRIs, which cause hyponatremia more frequently than other antidepressant drugs [27]. The incidence of hyponatremia caused by SSRIs varies widely from 0.06 % to 32 % [27, 28]. In the majority of cases, hyponatremia occurs within the first few weeks of the onset of therapy, whereas the normonatremia is achieved within 2 weeks after drug withdrawal. Older age, concomitant nonpsychiatric medication use, such as diuretics and angiotensin-converting enzyme inhibitors, as well as the presence of medical comorbidities are the most important contributory factors for the development of hyponatremia associated with SSRIs [27, 28, 37, 38, 49].

Finally, there is one well-documented case of lorazepam-induced hyponatremia, in which the development of hyponatremia was attributed to SIADH [50]. Benzodiazepines influence the neurotransmitter gamma-aminobutyric acid, which has been shown to interact with vasopressinergic neurons [51].

Anticonvulsants

Carbamazepine therapy has been frequently implicated in the etiology of hyponatremia [52–57]. Carmabazepine can induce hyponatremia by increasing ADH release from the neurohypophysis. It was also proposed that carbamazepine may cause hyponatremia by increasing renal sensitivity to normal plasma ADH concentrations [52–55]. This effect is possibly mediated through an increased aquaporin 2 expression [58]. Furthermore, hyponatremia caused by a reset osmostat syndrome variant of SIADH has

been described after treatment with carbamazepine [55]. The incidence of carbamazepine-induced hyponatremia varies considerably from 4.8 % to 41.5 %, depending on the patient population studied [55–57]. Specifically, the incidence of this electrolyte disorder is greater in the elderly or in subjects who simultaneously use other medications known to cause hyponatremia (mainly diuretics) [55–57]. It is noteworthy that the hyponatremic effects of carbamazepine correlated with carbamazepine dose, serum carbamazepine level, and lower initial serum sodium concentration [55–57].

Oxcarbazepine is structurally related to carbamazepine and is a useful drug in treating patients with the same seizure types, but it may have an improved toxicity profile. However, oxcarbazepine can induce hyponatremia more frequently and often to a greater degree than carbamazepine [59]. Of note, from 14 studies of oxcarbazepine therapy, hyponatremia (serum sodium concentration $<$ 135 mmol/L) was observed in 21.5 % of patients, while 2.7 % of them had serum sodium levels $<$ 125 mmol/L [60]. It appears that hyponatremia is a dose-dependent adverse event of oxcarbazepine. Moreover, the combination of oxcarbazepine with other anticonvulsant medications increases the risk of oxcarbazepine-related hyponatremia [61].

Finally, except for carbamazepine and oxcarbazepine, hyponatremia is occasionally associated with other antiepileptic drugs. Indeed, valproic acid and levetiracetam can cause hyponatremia, possibly because of SIADH and lamotrigine by potentiating renal tubule effects of ADH [62–64].

Antineoplastic and Immunomodulating Agents

A number of anticancer drugs have been shown to induce hyponatremia by impairing renal excretion of water. Specifically, cyclophosphamide can either potentiate the renal effect of ADH or it can increase its release centrally resulting in hyponatremia. This complication is mainly seen in high intravenous doses of cyclophosphamide (30–50 mg/kg), along with vigorous hydration with hypotonic fluids to prevent hemorrhagic cystitis. However, hyponatremia can also occur with lower doses of this alkylating agent (10–15 mg/kg). Administration of isotonic saline solution instead of using water is an appropriate measure to minimize the incidence of cyclophosphamide-induced hyponatremia [65, 66].

The vinca analogues vincristine and, less often, vinblastine can also produce SIADH resulting in hyponatremia [67–70]. It has been reported that SIADH is seen in 1.3/100,000 treated patients with vinca analogues [71]. These drugs alter the normal osmoreceptor control of ADH secretion through a direct toxic effect on the neurohypophysis and hypothalamic system. Peripheral neuropathy, which is often observed in patients with vinca alkaloid-related SIADH, is an indirect evidence for this neurological toxicity [67].

Cisplatin and carboplatin are potent and broadly used platinum-based chemotherapeutic agents used for a variety of cancers, including sarcomas, some carcinomas, lymphomas, and germ cell tumors. Hyponatremia associated with platinum

compounds is described more frequently with cisplatin, especially when it is given with large volumes of hypotonic fluids to prevent nephrotoxicity [70, 72, 73]. The possible underlying pathophysiological mechanisms by which cisplatin induces hyponatremia are SIADH and renal salt wasting [74]. The incidence of hyponatremia secondary to cisplatin can be as high as 43 %. However, it is difficult to define precisely given that the majority of cases described are in case reports [70, 72]. It should be emphasized that in patients with chemotherapy-related hyponatremia, chemotherapy-induced nausea may have an important role because nausea is one of the most potent stimuli to ADH secretion known in humans.

Immunomodulators, including interferon, interleukin 2, tacrolimus, and levamisole, as well as monoclonal antibodies, also were shown to induce hyponatremia [70, 75]. The underlying mechanism in the majority of cases is thought to be SIADH. Finally, methotrexate in high doses can cause hyponatremia. A toxic effect on the neurosecretory areas of the cerebrum, as well as alteration of the distribution of body fluid volumes, was proposed as a possible explanation of methotrexate-induced hyponatremia [76].

Opioids

Morphine and other opioids have often been implicated as a cause of hyponatremia. Interestingly, in a matched case–control study, the use of opioids was independently related to hospital-acquired hyponatremia (OR 2.9, 95 % CI 1.1–7.8) [77]. Given that opioids are usually prescribed for pain relief, and pain is a very potent stimulus for ADH secretion, this may explain their relationship with hyponatremia. However, these drugs can also cause hyponatremia by enhancing directly the ADH release [78]. In addition, indirect stimulation of ADH secretion caused by opiate-induced nausea or hypotension may occur.

Amphetamines

Abuse of 3,4-methylenedioxymethylamphetamine (MDMA), also known as ecstasy, is an increasingly recognized cause of severe hyponatremia that frequently is lethal. This electrolyte disorder is ascribed to increased ADH secretion from the hypothalamus and to excessive water intake as an attempt to counteract hyperthermia that is common in MDMA users. Furthermore, MDMA-related hyperthermia via increased sweat sodium losses may be involved in the pathogenesis of MDMA-induced hyponatremia [79–81].

Angiotensin-Converting Enzyme Inhibitors

It is known that angiotensin-converting enzyme (ACE) inhibitors in combination with furosemide were shown to correct hyponatremia in patients with congestive heart failure. On the other hand, ACE inhibitors per se have been also associated with the development of SIADH and/or hyponatremia. In fact, a handful of cases of ACE inhibitor-related hyponatremia were reported [82]. The pathogenesis of hyponatremia in these cases is not entirely clear. However, these medications inhibit the conversion of angiotensin I to angiotensin II in peripheral tissues, but not the brain. In the brain, angiotensin I is converted to angiotensin II, which may stimulate thirst and the release of ADH. Additionally, ACE inhibitors induce an increase in ADH secretion by delaying the degradation of bradykinin.

Amiodarone

Hyponatremia is a rare but potentially lethal adverse event of amiodarone therapy [83, 84]. Amiodarone-induced hyponatremia occurs mainly during the first weeks of therapy or even during the loading period. SIADH is the possible underlying mechanism through the channel-modulating properties of amiodarone on neural or renal tissues [83]. Of note, SIADH has been also described in association with other antiarrhythmic drugs, such as lorcainide and propafenone [85, 86].

Antibiotics

Antibiotic therapy has been rarely implicated in the etiology of hyponatremia [1, 87]. Specifically, trimethoprim–sulfamethoxazole (TMP–SMX, co-trimoxazole) can cause hyponatremia especially after administering high doses. TMP acts as a potassium-sparing diuretic by blocking the amiloride-sensitive sodium channels in the distal tubule. Consequently, the mild hyponatremia observed in patients receiving TMP should be ascribed to ongoing sodium losses resulting in hypovolemia and increased ADH secretion [88]. Pentamidine (another blocker of the aforementioned channels) has also been reported to cause hyponatremia. The precise mechanism of hyponatremia is not known. However, it is possible that the precipitous drop in blood pressure (that is often evident after the rapid administration of pentamidine) in combination with sodium renal losses may play a role [89, 90]. Furthermore, hyponatremia is a rare adverse effect of ciprofloxacin [91], rifabutin [92], or vidarabine therapy [93, 94]. SIADH is the possible underlying mechanism. A case of voriconazole-induced hyponatremia due to salt-losing nephropathy has been described [95]. Finally, hyponatremia following treatment with cefoperazone/sulbactam [96] and miconazole has also been reported [90, 97]. Remarkably, there

is some experimental evidence in rats that minocycline protects against neurologic complications of rapid correction of hyponatremia, suggesting its possible role in clinical practice [98, 99].

Proton Pump Inhibitors

Hyponatremia is a rare adverse effect of proton pump inhibitors (PPIs). The underlying pathophysiological mechanism of hyponatremia is not entirely clear, but is believed to be SIADH. In addition, salt-losing nephropathy due to PPIs-induced acute interstitial nephritis might be at play [100].

Theophylline

Theophylline-induced hyponatremia has rarely been described. Theophylline possesses a thiazide-like action inhibiting solute reabsorption in both the proximal nephron and diluting segment. Furthermore, SIADH and the concurrent hypokalemia, especially in patients with acute intoxication, may play a contributing role in the development of theophylline-associated hyponatremia [101].

Hypoglycemic Agents

Chlorpropamide, which is now rarely used in the treatment of patients with diabetes mellitus, can cause hyponatremia in approximately 4 %–6 % by potentiating the effect of ADH. Elderly patients concomitantly using diuretics have greater risk of developing hyponatremia [102–105]. Tolbutamide can lead to hyponatremia by decreasing renal free water clearance [104]. Furthermore, insulin has been implicated in hyponatremia [77]. The exact mechanism of this association remains unknown but may be related to an interaction between insulin and vasopressin, both of which act in the renal collecting duct [106]. Noteworthy, despite the fact that fluid retention is a common adverse effect of both thiazolidinediones (pioglitazone and rosiglitazone), hyponatremia related to these drugs was reported only once [107].

Nonsteroidal Anti-Inflammatory Drugs

Nonsteroidal anti-inflammatory drugs (NSAIDs) decrease water excretion by potentiating the effect of ADH. This is mediated by a reduction in renal prostaglandin synthesis, since prostaglandins normally antagonize the action of ADH.

It should be illustrated that hyponatremia attributable exclusively to NSAIDs is rare, probably because prostaglandin inhibition also may directly suppress ADH secretion centrally. However, these agents may exacerbate the tendency to hyponatremia in volume-depleted patients or in those with SIADH [108, 109].

Exogenous Administration of ADH

Oxytocin, used to induce labor or abortion, having significant antidiuretic activity can induce hyponatremia when administered with excess electrolyte-free water [110, 111]. This complication can be prevented by limiting the amount of water given and using isotonic saline, rather than dextrose and water. Moreover, hyponatremia is a possible consequence after administering exogenous ADH (as part of the treatment of patients with gastrointestinal hemorrhage) or desamino-8-D-AVP (an analogue of ADH), which is used for either polyuria in patients with central diabetes insipidus or bleeding caused by platelet dysfunction (von Willebrand disease) [112, 113]. Finally, hyponatremia is common in patients with severe gastrointestinal bleeding due to portal hypertension treated with terlipressin a drug which is converted to ADH in vivo [114].

Mannitol

In some cases of hyponatremia, decreases in serum sodium levels are associated with normal or increased effective plasma osmolality, rather than hypoosmolality. Administration of hypertonic mannitol is an example of hyponatremia with increased plasma osmolality. Mannitol (by increasing plasma osmolality) creates a transcellular osmotic gradient, resulting in water movement out of the cells and decrease in serum sodium concentration by means of dilution. This was called dilutional or translocational hyponatremia.

Immune Globulin

It is well known that hyperlipidemia or hyperproteinemia can induce pseudohyponatremia. Furthermore, intravenous infusion of immune globulin increases the protein-containing nonaqueous phase of plasma, with a consequent relative decrease in plasma water volume. Because sodium is present in only the aqueous phase, each unit volume of plasma measured has less sodium containing water, and this is interpreted as hyponatremia. Newer methods using ion-selective electrodes for the measurement of serum electrolytes may avoid this problem and give accurate results if measured in undiluted samples (direct potentiometry).

Intravenous immune globulin frequently is administered in a 10 % maltose solution. Maltose normally is metabolized by maltase in proximal tubules. However, in patients with renal failure, maltose accumulates in extracellular fluid, increasing plasma osmolality and diminishing serum sodium levels by means of dilution [115]. Translocational (hyperosmotic) hyponatremia also can be observed with sugar-containing intravenous immune globulin administration. It appears that the magnitude of hyponatremia depends considerably on the degree of renal impairment during intravenous immune globulin infusion. In the setting of impaired renal function, decreased renal clearance of sucrose takes place, leading to increased effective plasma osmolality [116].

Finally, intravenous administration of immune globulin also can cause hyponatremia because of aseptic meningitis-related SIADH [116].

Treatment–Recommendations

Although medications are one of the most frequent causes of hyponatremia, most of the agents listed in Table 6.1 are only rarely associated with the development of low serum sodium levels. However, it is entirely clear that careful oversight of the use of implicated agents is required given that even mild hyponatremia can have adverse outcomes (increased mortality, cognition impairment, high risk of falls and fractures). Consequently, in cases of drug-induced hyponatremia, discontinuation of therapy with these agents and avoidance of readministration is fully warranted. Moreover, in euvolemic patients who present with severe symptomatic hyponatremia, the treatment consists of hypertonic sodium chloride solution (3 %) administration, along with water restriction. In patients with extracellular volume depletion (e.g. due to diuretics), normal saline solution with or without potassium chloride should be administered intravenously to correct hypovolemia and hypokalemia, if present.

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Chapter 7
Hyponatremia in Heart Failure

Mohammad Sarraf and Steven R. Goldsmith

Background

A common feature of heart failure (HF) is salt and water retention. Hyponatremia, defined as a serum sodium concentration <135 mmol/L, is a frequent finding in HF patients admitted to the hospital. Hyponatremia is present in 8–27 % of patients as reported in various recent registries and clinical trials [1–4]. Hyponatremia is multifactorial in origin with potential causes including neurohormonal activation, hemodynamic instability, HF-related renal derangement, and possibly therapies applied to treat HF. Most cases of hyponatremia in HF occur with normal or expanded total blood volume and so are due in large part to the presence of excessive levels of the antidiuretic hormone arginine vasopressin (AVP). The presence of hyponatremia clearly correlates with disease severity and outcome. Many models have identified hyponatremia as an independent negative prognostic variable [5, 6]. This relationship is independent of renal function. In this chapter, we will review the importance of hyponatremia in patients with HF as a marker of severity and as a potential target of therapy, as well as the status of the most recent development in therapy for hyponatremia in HF, antagonism of the V2 receptor for AVP.

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Prevalence and Prognostic Importance

The actual prevalence of hyponatremia in HF is not entirely clear. The reported prevalence of hyponatremia is dependent on the cutoff values applied for hyponatremia, the severity of HF, and the frequency of testing during hospitalization. Moreover, the frequency of hyponatremia is known to be under-reported on the discharge diagnosis [7]. For example, in one report only 30 % of patients with severe hyponatremia had an ICD-9 code on discharge [7].

Despite the limitations in the data, hyponatremia is relatively common in HF registries and randomized control trials. In the Acute and Chronic Therapeutic Impact of a Vasopressin in Congestive Heart Failure (ACTIV-CHF) study, the incidence of hyponatremia—defined as sodium concentration less than 136 mmol/L—was approximately 20 % [8]. Klein et al. have reported an incidence of hyponatremia, defined as serum sodium concentration of less than 135 mmol/L, of 27 % in the Outcomes of Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure (OPTIME-CHF) [1]. In the Evaluation Study of Congestive Heart Failure and Pulmonary Artery Effectiveness (ESCAPE) trial [9], 23 % of patients had hyponatremia defined as serum sodium concentration of <134 mmol/L. However, the Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study with Tolvaptan (EVEREST) demonstrated an incidence of 8 % (serum sodium concentration <135 mmol/L) in patients with HF. This low incidence may be reflective of the inclusion criteria of the study [4, 10].

While the incidence of hyponatremia may not be entirely consistent, all studies to date have confirmed a poor outcome in HF patients with hyponatremia. This is true for patients with chronic HF on appropriate medications [11]. In hospitalized patients a low serum sodium concentration on admission or discharge correlates with worse in-hospital [12, 13], short-term [1], and long-term mortality [14]. Moreover, it is associated with an increased rate of readmission [15], other major complications, [12] and a longer length of stay in patients admitted for HF [16]. Regarding the magnitude of the impact of the presence of hyponatremia subanalysis of the Acute and Chronic Therapeutic Impact of a Vasopressin Antagonist in Chronic Heart Failure (ACTIV-CHF) trial, involving 319 patients, demonstrated a fivefold higher risk of death in 60 days in patients with hyponatremia when defined as sodium concentration <136 mmol/L [8]. A Cox proportional hazards analysis of OPTIME-CHF demonstrated an increase of 18 % in 60-day mortality of patients with each 3 mEq/dl decrement of serum sodium concentration on admission [1]. And in one of the largest studies addressing this issue, the Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure (OPTIMIZE-HF) registry, Gheorghiade and colleagues demonstrated a marked correlation between serum sodium concentration <135 and number of days in the hospital, in-hospital mortality, and post-discharge mortality [3] (Table 7.1). The investigators also observed an apparent "U" shape curve with in-hospital mortality, with increasing mortality if the serum sodium was greater than 140 mmol/L (Fig. 7.1). In this registry there was no association between

Table 7.1 Relationship between clinical outcomes in patients hospitalized for HF and serum sodium concentration

	Days in the hospital	Mortality in-hospital	Mortality post-discharge	Death or readmission since discharge
Sodium ≤135*	6.4	6	12.4	42.5
Sodium >135	5.5	3.2	7.1	34.8

*$P < 0.001$ for all variables [3]

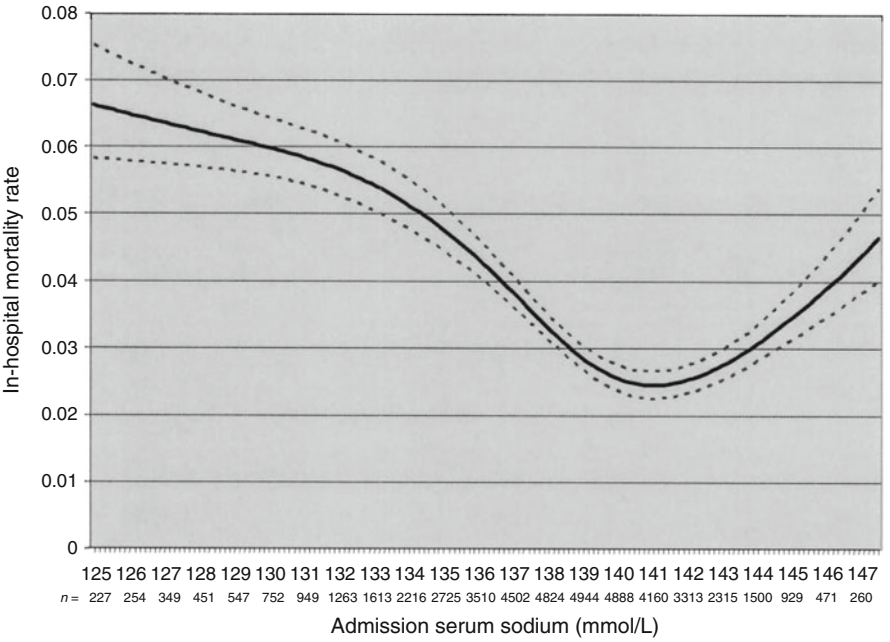

Fig. 7.1 Relationship between admission serum sodium level and in-hospital mortality. Restrictive cubic spline transformation plot with 95 % confidence intervals is shown. (By permission of Oxford University Press [3])

hyponatremia and rehospitalization. Finally in chronic HF a multivariate Cox model analysis of an observational study within the Duke Databank for Cardiovascular Disease, hyponatremia was associated with an increase in all-cause death (HR = 1.42, 95 % CI = 1.07–1.88) and cardiovascular death/rehospitalization (HR = 1.45, 95 % CI = 1.14–1.86) [11].

Fewer studies are available which have examined the prognostic impact of a rise in serum sodium following admission to the hospital. There are no prospective randomized trials addressing this issue, and the retrospective reports differ. In an analysis from the ACTIV trial, improvement in hyponatremia was linked to improved 60-day outcomes, and most of the improvement in serum sodium was

in the group treated with tolvaptan [8]. A study by Madan et al. [17] also showed a relationship between improvement in serum sodium and lower mortality. However, in the ESCAPE trial, an improvement in serum sodium was not associated with an improvement in outcomes though there was a trend [9]. These reports were all based on relatively small numbers of patients. A large recent registry report from Korea by Lee et al. [18] following 2,888 patients for up to 1.7 years found that there was no mitigating effect of an improvement in serum sodium on later mortality if hyponatremia was present at admission. In contrast to, at least, the study by Madan, only a predischarge sodium in this registry was reported as follow up, suggesting that an improvement in outcome from improving serum sodium might take more time to demonstrate. These studies were all retrospective analyzes of either trials or registries and did not include protocols specifically directed at treating hyponatremia. To settle the issue of whether improvement of hyponatremia improves outcome in HF would require a prospective, randomized, placebo-controlled trial in hyponatremic patients, preferably with therapy shown to be safe and effective in this condition [8, 19]. A recent report linking chronic hyponatremia to increased fibrosis in myocytes may lend further support for such a trial [20].

Pathophysiology of Hyponatremia in HF

Sodium and water retention and resultant edema formation are cardinal features of chronic HF. The inability to adequately excrete sodium has long been established as a marker of clinical HF [21]. Hyponatremia is a result of an imbalance between total body sodium and water, irrespective of total body sodium content. In HF where the plasma volume is normally expanded, hyponatremia is normally characterized by an overall excess of both sodium and water with the increase in total body water being greater than that of sodium [22, 23].

In any setting, hyponatremia ultimately involves failure to maximally dilute the urine [22, 23]. Maximum urinary dilution requires three essential components. First, the antidiuretic hormone (AVP) should be absent. Second, there must be adequate delivery of free water to the distal and collecting tubules; and third, there must be normal function of the loop of Henle in order to create the osmotic gradient by which water is reabsorbed distally in the absence of AVP. Only in settings of massive water intake can the normal capacity of the kidney to dilute the urine be overcome. In HF, derangements in all three factors are frequently found, making the etiology of hyponatremia complex and variable depending on the specific patient [22, 23].

Increased levels of plasma AVP are commonly observed in patients with HF [24–26], particularly those with more advanced disease in whom hyponatremia is more commonly seen. The cause of the increased AVP levels in HF remains elusive, but is probably related to the generalized state of neurohormonal imbalance, since both Ang II and NE are capable of stimulating AVP release [27]. In one of the original descriptive series of AVP levels in HF, there was a significant

positive correlation between plasma AVP and plasma renin activity [25]. Also, in a more recent series of patients with HF in whom AVP was measured, levels were much lower than in prior studies, despite nearly identical hemodynamics [28]. The major difference between the newer and older series was the use of neurohormonal antagonism as background therapy in the patients in the more recent report. This difference would accord with the notion that differences in central "drive" from diminished angiotensin II and NE levels account for the lower AVP levels in the more recent series, despite a similar hemodynamic profile.

The more "conventional" explanation for this nonosmotic drive cites hemodynamic factors operating via the low and high pressure baroreflexes [29]. But while AVP is very sensitive to increases and decreases in afferent input from these reflex systems in animals such as dogs and rats, it is much less sensitive to such perturbations in humans and monkeys, particularly to input from the low-pressure cardiopulmonary receptor system [30]. Sustained decreases in central venous pressure and moderate decrease in arterial blood pressure are without effect on plasma AVP in normal humans and also in monkeys [31–33]. Increases in blood volume and pressure do not suppress basal AVP levels in normal humans and monkeys, and improving cardiac output also does not decrease elevated AVP levels in human HF [25, 34–36]. Teleologically, this diminished sensitivity of AVP to baroreflex tone makes sense since if AVP was as responsive to changes in baroreflex tone in bipeds as it is in quadrupeds, it would be very difficult to maintain appropriate water balance under the full range of normal operating conditions for these reflexes. It has, however, been shown that severe acute hypotension will release AVP in primates as shown in experiments with graded hemorrhage in monkeys [33], so perhaps in critically ill patients with low arterial pressure and/or very low cardiac output, these receptors may play a role. Since most patients with elevated AVP levels are neither hypotensive nor in a low cardiac output state, it would seem unlikely that the baroreceptors are influencing basal AVP levels in the broader run of HF patients. Regardless of the precise nature of the nonosmotic drive for AVP secretion, when AVP levels do rise, increased AVP signaling at the renal V2 receptor is likely to be the key element in the production of hyponatremia. The robust response of hyponatremic patients to the administration of V2 antagonists (see below) validates this assertion. Yet, the administration of these agents frequently does not fully correct the serum sodium, which attests to the possible impact of other factors.

Adequate delivery of water to the diluting segment can be prevented by intense proximal reabsorption of salt and water and/or by very low flow rates. Increased proximal reabsorption of salt and water can occur in the setting of low blood pressure or very low cardiac output, but as noted above, most patients with HF and hyponatremia are not hypotensive or in a low output state. However, virtually all patients with HF have activation of the RAAS and SNS, and both Ang II and NE directly constrict the renal circulation and promote proximal reabsorption of salt and water, in addition to potentially stimulating AVP release [29]. Depending on the activity of the RAAS and SNS, impaired solute delivery can therefore contribute to hyponatremia in HF, especially if this occurs in the setting of inappropriate AVP release.

Finally, many patients with HF are on loop diuretics, although increased AVP levels were reported even in the SOLVD Prevention patients, who had low ejection fractions but no clinical HF and were not on diuretics [37]. If a loop diuretic is present, however, it is impossible for the kidney to generate maximally dilute urine due to the presence of increased sodium in the fluid delivered to the distal tubule. Therefore, in patients treated with loop diuretics, it may be particularly difficult to treat hyponatremia, especially if the patient is intensely vasoconstricted and has elevated AVP levels [38]. The fact that furosemide causes neurohormonal activation [39], including the direct or indirect stimulation of AVP, and that this is not completely blocked even in the face of angiotensin-converting enzyme inhibitors [40], makes the presence of this agent particularly problematic in hyponatremic patients. Yet, it may be necessary to facilitate decongestion.

In summary, the pathophysiology of hyponatremia in HF is complex and likely involves many variables. The precise contribution of each variable will differ depending on the hemodynamic and neuroendocrine state of a particular patient. Striving in general to optimize hemodynamics, diminish neuroendocrine imbalances, block the effects of Ang II and NE, antagonize the V2-mediated effects of AVP, and limit the use of loop diuretics all may contribute to mitigating the various factors that contribute to this condition.

Treatment of Hyponatremia in HF

Treatment of hyponatremia in HF is similar to that in other conditions. The astute clinician starts by evaluating the patient's volume status. As noted earlier, serum sodium concentration does not, by itself, give any clue as to the volume status of the patient. If the patient is hypovolemic, hyponatremia will respond to the administration of normal saline. This can be seen in patients with HF if they are overdiuresed. In most other settings, absent a drug or disease known to stimulate AVP release, hyponatremia in HF will be associated with an expanded blood volume since as noted, the generalized state of neurohormonal activation seen in advanced HF includes NE, angiotensin II, aldosterone, as well as AVP, all of which contribute to retention of sodium and thus an expansion of blood volume. The only alternatives for treating hyponatremia when blood volume is expanded are to restrict water intake or interfere with the retention of free water. The former approach is difficult and rarely tolerated given the stringency of the required restriction. Regarding the latter approach, if the retention of free water is due to excessive AVP secretion, then from a pathophysiologic standpoint, therapy could involve inhibition of AVP release, interference with the activation of the V2 receptor by AVP, or inhibition of the effects of V2 receptor activation on the tubule. At present there are no agents which suppress AVP release other than ethanol (which is not for obvious reasons a good therapeutic choice, and which, interestingly, has been shown not to suppress

AVP release in patients with HF) [41]. There are as yet no proven methods of safely interfering with the effects of V2 activation on the tubule, hence the most viable, and to date the only proven therapeutic strategy, is to interfere with AVP-mediated activation of the V2 receptor.

Fluid Restriction

In the absence of more targeted therapy, fluid restriction has been an important strategy in the treatment of all euvolemic and hypervolemic forms of hyponatremia, yet it has limited utility and has never been subjected to a randomized controlled trial for either efficacy or safety in HF. When this strategy is used, fluid intake should be limited to such a degree that a negative balance state arises relative to potential sources of free water gain. This is particularly challenging in hospitalized patients who often have higher thirst drive as a result of various therapies and neurohormonal stimulation, as well as high obligate fluid intake from concomitant therapy. In most cases, total fluid intake should be kept to $<$1,000 mL. Most HF patients have difficulty adhering to such a restrictive prescription due to their thirst drive, possibly linked to elevated angiotensin II levels. Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) have demonstrated only limited success in ameliorating thirst [42].

Renin–Angiotensin–Aldosterone (RAAS) Blockade

Since RAAS activation is one of the key mechanisms of HF progression and worsening, it is intuitive that blockade of this system would be a target since as noted an activated RAAS could influence both renal blood flow, the direct reabsorption of sodium and water and as well, stimulate AVP secretion. The use of ACE inhibitors or ARBs may in fact have an effect on mild hyponatremia. Normalization of sodium can be accelerated in this situation and in more marked hyponatremia by concomitant hypotonic fluid restriction, discontinuation of any thiazide diuretic, and/or addition of a loop diuretic [43]. The improvement in hyponatremia with these drugs is most likely related to decreased stimulation of AVP by angiotensin II as well as improving GFR and improving proximal sodium and water handling [44]. These beneficial effects of ACE inhibitor or ARB therapy are seen as long as renal perfusion is not compromised by a fall in blood pressure. Since hyponatremic patients often do have elevated levels of plasma renin activity, they are more susceptible to the hypotensive and azotemic effects of ACE inhibitors [45]. Thus, when these RAAS-inhibiting drugs are used, one must avoid hypotensive episodes [46].

Diuretic Therapy

Diuretic therapy in the HF patients with hyponatremia is particularly challenging. Unless an inhibitor of the V2 receptor is given, diuretics often need to be at least temporarily withdrawn in order to remove their effects on worsening hyponatremia. Yet these patients normally require diuretics to overcome volume overload. If this is required, thiazide-type diuretics should be avoided and loop diuretics preferably given to favor free water clearance. These agents will produce hypotonic urine and should in theory always result in an increase in serum sodium. But the adverse neurohormonal and hemodynamic effects of loop diuretics, including the stimulation of AVP, may offset this beneficial effect on water excretion and so lead to a worsening of the serum sodium despite persistent congestion [47]. This phenomenon is well known to clinicians caring for patient with severe HF.

Lithium, Demeclocycline, and Urea

Indirect inhibition of the AVP receptor-mediated retention in free water was reported as early as 1970s, when lithium (Li^{2+}) was the only drug available to treat the syndrome of inappropriate antidiuretic hormone (SIADH) [48]. Li^{2+} inhibits the antidiuretic action of AVP by reducing V2 receptor-mediated stimulation of adenyl cyclase, prior to the engagement of the aquaporin 2 channels. Thus, free water clearance increases. Patients with SIADH had a marked improvement in their serum sodium concentration within a few days of starting Li^{2+}. The drawbacks of this approach, however, were many. For instance, glomerular filtration rate (GFR) can affect the pharmacokinetics of the drug and older age increases the risk of neurotoxicity [49]. Furthermore, ACE inhibitors and ARBs may increase the risk of Li^{2+} toxicity [50]. For these reasons, the risk profile lithium is not ideal in clinical practice especially in HF patients in whom older age, abnormal kidney function, and RAAS blockers usage are common. The use of lithium for hyponatremia in HF has never been evaluated in a randomized controlled trial.

Another agent that enjoyed attention in treating patients with hyponatremia is demeclocycline. It is a tetracycline derivative, which diffusely interferes with tubular function and so reduces the antidiuretic effect of AVP more effectively than Li^{2+}. It usually takes 2–4 days for the maximum effect of any dose [23]; therefore, frequent modification of the dosage on a daily basis should be avoided until the drug reaches the steady state. Renal function should be monitored if the patient is chronically treated with demeclocycline, for it can cause reversible azotemia and, at times, may be overtly nephrotoxic, particularly in patients with cirrhosis [23, 51]. These features of this drug make it an unsuitable candidate in patients with severe HF who often have abnormal renal function. As with lithium, there are no controlled trials data for its use in the hyponatremia of HF.

Urea will force a water diuresis, which may help in improving serum sodium, but it has significant issues around tolerability. Like lithium and demeclocycline, urea has never been subjected to a randomized controlled trial in the hyponatremia of HF and, again like the other agents, is not approved by regulatory authorities for this purpose.

Vasopressin Receptor Antagonists

Excessive AVP secretion is, as noted, common in patients with HF including those with hyponatremia [24–26]. As discussed earlier, AVP likely plays the major role in abnormal water metabolism in patients with HF. Therefore, it seems intuitive that blocking the V2 receptors which mediate water retention (see below) should be a target of therapy for hyponatremia treatment in HF, while the V1a receptor is the more logical target for the ventricular dysfunction and remodeling which characterize most patients with a HF syndrome [52–54]. Blocking the V2 receptor could also improve outcomes by treating hyponatremia and also by facilitating decongestion. The use of V2 antagonists in the absence of hyponatremia has shown consistent effects on weight loss in HF, but has not altered outcomes as shown in EVEREST [4, 10]. The development of nonpeptide vasopressin receptor antagonists offers for the first time a viable, pathophysiologically sound treatment strategy for hyponatremia in HF [55–57]. Three drugs in this class have been evaluated thus far: conivaptan, lixivaptan, and tolvaptan [58]. Conivaptan and tolvaptan are currently approved by the FDA in the USA for the treatment of euvolemic and hypervolemic hyponatremia, while lixivaptan is still under development. These drugs have all been shown to be effective in improving renal water handling and hyponatremia in conditions associated with water retention including HF. The safety profile of the two medications now available for clinical use is excellent.

Pharmacology of AVR Receptor Antagonists

AVP signals via at least three distinct receptors, V1a, V1b (aka. V3), and V2 [58, 59]. All are G-protein coupled receptors. Extracellular binding of AVP to V1a and V1b receptors results in hydrolysis of phosphatidylinositol to diacylglycerol and inositol triphosphate, an increase of intracellular calcium, and activation of protein kinase C. Binding to the V2 receptors leads to activation of adenylyl cyclase, generation of cAMP, activation of protein kinase A, which promotes the translocation of aquaporin-2 water channels from basolateral location of principal cells to the luminal membrane, increasing free water absorption [58]. V1a receptors are present on smooth muscle cells of the vasculature and when activated classically produce vasoconstriction. More recently it has been shown that V1a receptors are present on myocardial cells and

when activated produce an increase in protein synthesis and hypertrophy [60]. V2 receptors are mainly located in the kidneys where their main effect is to activate the aquaporin 2 protein as already mentioned. In endothelial cells their activation may cause vasodilation via nitric oxide synthase stimulation [61].

V2 receptor antagonists are known as aquaretics, as their key action is to oppose the reabsorption of free water. This is the fundamental difference between these agents and standard diuretics which inhibit sodium reabsorption and thus indirectly inhibit water reabsorption. However, with loop diuretics, the mainstay of volume control strategies in HF, inhibiting sodium reabsorption in the loop of Henle increases sodium delivery to the juxtaglomerular apparatus, leading to a reduction in GFR via tubule-glomerular feedback [62]. This is not a concern with V2 antagonists.

Tolvaptan

The effect of tolvaptan as monotherapy for fluid balance was evaluated in 83 patients with HF (NYHA Class II–III) in a randomized, controlled trial [2]. Patients were removed from baseline diuretics and randomized to four groups. One group received placebo ($n = 21$), the second group was randomized to either monotherapy with tolvaptan 30 mg ($n = 20$) or monotherapy with furosemide 80 mg ($n = 22$). The fourth arm of the study received both tolvaptan and furosemide ($n = 20$). Tolvaptan was given once daily for 7 days. Tolvaptan reduced body weight and reduced edema without concomitant diuretic therapy compared with placebo.

The acute and chronic therapeutic impact of tolvaptan as adjunctive therapy to loop diuretics in congestive heart failure (ACTIV in CHF) trial was conducted in 319 hospitalized patients with CHF with left ventricular ejection fraction of less than 40 % [8]. Patients received tolvaptan orally at doses of 30, 60, or 90 mg/day up to 10 days as an inpatient. All patients were followed for up to 60 days as an outpatient. Body weight at 24 h following the dosing was markedly reduced in all three doses of tolvaptan-treated subjects compared with placebo (-1.8, -2.10, and -2.05 kg for the 30-, 60-, and 90-mg groups, respectively; $P < 0.008$ in all groups). Tolvaptan also improved serum sodium levels in patients with hyponatremia. The primary endpoint of death, rehospitalization, or unscheduled visits for HF at 60 days did not differ between the groups (26.7 % vs. 27.5 %, $P = 0.88$). Tolvaptan treated patients had increased incidence of thirst sensation. No abnormalities in cardiac function or worsening of renal function occurred during use of tolvaptan. As already noted there was an association of improved serum sodium with improved mortality in this study.

The study of ascending levels of hyponatremia 1 and 2 (SALT-1 and SALT-2), were two identical trials (one carried out in the USA and the other at international sites) and randomized patients with hyponatremia due to SIADH, chronic heart failure, or cirrhosis to oral placebo ($n = 223$) or oral tolvaptan ($n = 225$) at a dose

of 15 mg daily for up to 30 days [63]. The maximal dose of the study drug could be increased up to 60 mg daily during the first 4 days. Serum sodium concentrations rose more in the tolvaptan group than in the placebo group during the first 4 days ($P < 0.001$) and after the full 30 days of therapy ($P < 0.001$). This study suggested that in patients with euvolemic or hypervolemic hyponatremia, tolvaptan was effective in increasing serum sodium [63]. The increase in serum sodium was similar irrespective of the underlying disease process. This points to the pivotal role of AVP in the genesis of hyponatremia in each condition.

The efficacy of vasopressin antagonism in HF outcome study with tolvaptan (EVEREST) trial evaluated 4,133 patients hospitalized with worsening HF and with subjective and objective evidence of fluid overload [4, 10]. Patients were randomized 1:1 to tolvaptan 30 mg/day or placebo for a minimum of 60 days. Adverse events resulting in study drug discontinuation occurred in 6.5 % of tolvaptan patients. The most common adverse events were thirst and dry mouth. During a median follow-up of 9 months, tolvaptan did not affect all-cause mortality or the combined end point of cardiovascular mortality, or subsequent hospitalization for worsening HF [4, 10]. There were no hemodynamic safety concerns such as hypotension, tachycardia, or worsened renal function. Therefore, while tolvaptan was safe over the long term in a large population of patients with HF, it did not change the outcomes. Based on data from these definitive clinical trials, V2 receptor antagonism with tolvaptan does not seem to affect the progression of the overall HF condition, despite improving fluid retention and hyponatremia when present.

Analysis of the hyponatremic subset within EVEREST did, however, demonstrate a persistent benefit on hyponatremia. There were more patients in this subset than in the entire SALT trial, so the efficacy and safety of the use of tolvaptan in the treatment of hyponatremia in HF is well established. As was the case in the ACTIV trial, a posthoc analysis of the effects of tolvaptan in patients with serum sodium concentration <130 meq/L demonstrated improvement in cardiovascular morbidity and mortality [64]. These results can be considered to be a hypothesis generator since the EVEREST trial did not randomize the patients based on sodium level. However, findings of sustained reduction in body weight, without worsening of renal function and with sustained normalization of serum sodium levels in patients with baseline hyponatremia, could suggest a role for either longer term or intermittent tolvaptan treatment in these patients.

The reasons why tolvaptan failed to improve cardiovascular outcomes in the population as a whole, despite a reduction in body weight, remain uncertain. Several possibilities have been proposed. First, it is likely that the dose of tolvaptan (30 mg/day) may have been inadequate; second, most patients did not have hyponatremia (89 % of the cohort); and third, the possibility that a reactive increase in vasopressin levels might, over the long term, have stimulated the V1a receptor, causing an offsetting adverse effect which might negated any beneficial effects associated with aquaresis [57]. Also, in this regard, it has been recently been shown stimulation that V1a receptor activation causes the adrenal production of aldosterone [65]. The V1a receptor may also affect the renal tubular effects of aldosterone [66]. Only a minority of patients in the EVEREST trial were on aldosterone antagonists.

Conivaptan

Conivaptan blocks V2 and V1A receptors. In a small study of eu- and hypervolemic patients with hyponatremia of 115–<130 mEq/L, 84 patients were randomized to placebo or conivaptan (40 or 80 mg/day) for 4 days [67]. Serum sodium concentration was increased on day 1 with either dose of the conivaptan ($P < 0.001$). Also, the effective water clearance on day 1 improved when compared with placebo ($P < 0.05$). Conivaptan was well tolerated throughout the study, but conivaptan was associated with injection site reactions [67].

Subsequently, pooled data from three phase III trials were combined and the effect of conivaptan in the subset of patients with CHF was analyzed [68]. The investigators found 94 patients with HF out of the 241 patients enrolled in these studies. These studies compared the efficacy of intravenous and oral form of conivaptan. In the intravenous trial, patients received a 20-mg I.V. loading dose of conivaptan or placebo followed by continuous infusion of the drug or placebo at 40 or 80 mg/day for 4 days. In the two oral trials, patients received 40 or 80 mg/day or placebo in two divided doses for 5 days. There was an improvement in serum sodium concentration from baseline to the end of study compared with placebo. While all patients had improved serum sodium level, the rate of rise in HF patients was slower than non-HF patients. Adverse events included headache, nosebleed, pyrexia, worsening CHF, renal failure, and infusion site reactions in the IV trial. Despite the beneficial effect of oral conivaptan, this formulation is currently not available due to significant cytochrome P-450 interaction.

In a dose-ranging pilot study of patients with acute decompensated HF, conivaptan effectively increased urine output with a parallel decrease in body weight. This finding was additive to that seen with standard loop diuretic therapy alone [53]. These patients did not, however, have an appreciable incidence of hyponatremia.

The hemodynamic effects of a single IV dose of conivaptan (10, 20, or 40 mg) were studied in 142 patients with symptomatic NYHA class III–IV HF with normal serum sodium [28]. Compared with placebo, conivaptan 20 and 40 mg significantly reduced pulmonary capillary wedge pressure and right atrial pressure. There was also a parallel and significant dose-dependent increase in urine output and decrease in urine osmolality. This study establishes the beneficial acute effect of combined V1A and V2 antagonism on hemodynamics and free water excretion in HF.

Lixivaptan

Lixivaptan is an orally active V2 receptor antagonist that lowers urine osmolality and increases serum sodium concentration [58]. In one study, different doses (25, 125, or 250 mg twice daily for seven consecutive days) of lixivaptan were evaluated in a diverse population with hyponatremia (<130 mmol/L for three

consecutive days) due to HF, cirrhosis, and SIADH [69]. A significant improvement in free water clearance was noted with the two highest doses of lixivaptan with no significant changes in renal function or hemodynamics. However, five patients (50 %) taking 250 mg of lixivaptan twice daily had to have medication withheld on multiple occasions during this 7-day trial because of significant dehydration, as indicated by increased thirst and marked increases in serum sodium concentration. It is noteworthy that the aquaretic effects of lixivaptan plateaued with repeated administration, particularly with the higher doses. It is postulated that increased AVP levels may be related to this effect [69].

When to Treat Hyponatremia in Heart Failure

As reviewed elsewhere in this book, the symptoms of mild to moderate hyponatremia are quite nonspecific and overlap those of the conditions in which hyponatremia is frequently seen [51]. The only way to be certain that symptoms such as nausea, confusion, or gait instability are actually caused by hyponatremia would be to treat the hyponatremia directly and assess the response. This is now possible to do successfully in many patients given the introduction of vasopressin antagonists, but it should be noted that so far there are no outcomes data which establish a clinical benefit of treating either the symptoms of hyponatremia, or hyponatremia itself. Therefore, the decision to treat based on symptoms or on an absolute level of hyponatremia must be individualized. One situation specific to HF, however, may deserve comment. It is frequently the case that patients with severe HF will experience further declines in serum sodium when undergoing diuresis with loop diuretics, sometimes to ranges that are clearly problematic. This occurs due to the severity of the HF limiting flow to the diluting segment of the kidney, intense proximal renal arterial vasoconstriction, and possibly to the stimulating effect of loop diuretics on AVP release as discussed above. Under these circumstances the clinician must often choose between reducing the intensity of diuresis, thereby leaving the patient in a congested state, or further worsening hyponatremia to potentially dangerous levels. Without an effective treatment for hyponatremia the situation is often resolved by reducing the diuretic dose. Leaving patients in a congested state, however, is associated with poor outcomes and should be avoided. For this reason, while specific data have not been obtained to support benefit of this approach in this type of patient in clinical trials, strong consideration should be given to treatment of hyponatremia in such conditions to avoid undertreatment of the HF state. Since vasopressin antagonists have been proven to be safe and effective in the hyponatremia accompanying acute decompensated HF, the use of these agents under such circumstances would be rational, particularly since they will improve serum sodium and at the same time produce an incremental diuresis. If the choice lies between low sodium and persistent congestion or improved sodium with diminished congestion, both theoretical and empiric considerations would favor the latter scenario. To fully establish benefit, however, a randomized trial of treatment or nontreatment under those specific conditions would be necessary.

Conclusion

Hyponatremia is a relatively common finding in patients with HF and is consistently associated with poor outcomes. Although there are a number of potentially helpful treatments for hyponatremia in HF, the only therapy which has been subjected to rigorous testing, and the only therapy which has received approval by the United States Food and Drug Administration for this condition is based on antagonism of the V2 receptor for AVP. Conventional approaches such as fluid restriction do not work well and/or are not well tolerated. Other drugs such as urea and demeclocycline have major side effects and/or are quite toxic. Hyponatremia in HF may be transient and associated with overall decompensation with acute neurohormonal imbalance, and so when hemodynamics improve along with symptoms, neurohormonal imbalances may improve as well, and hyponatremia may improve without specific-targeted treatment. But when hyponatremia worsens despite conventional treatment, or persists despite such treatment, V2 antagonism has been proven to an effective and safe strategy for its correction. Many questions remain to be answered regarding the potential benefits of treating mild to moderate hyponatremia in HF, in particular any impact on outcomes.

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Chapter 8
Hyponatremia in Cirrhosis: Evaluation and Treatment

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Patients with end-stage liver disease and ascites have a functional renal impairment that render the kidney susceptible to retain sodium and solute-free water [1]. In some patients, this disorder leads to a disproportionate retention of water relative to sodium which leads to a dilutional state where water is retained out of proportion to sodium causing hyponatremia and hypoosmolality. Hyponatremia in the general population is defined as a serum sodium level below 135 mEq/L [2]. However, hyponatremia in cirrhosis has been defined as a serum sodium concentration of less than 130 mEq/L in the presence of ascites or edema [3–5]. A significant proportion of patients with cirrhosis have a serum sodium concentration above 130 mEq/L and below 135 mEq/L; however these patients may display pathogenic and clinical features similar, yet less pronounced, to those of patients with serum sodium below 130 mEq/l. In patients with cirrhosis and ascites the 5-year probability of developing hyponatremia is 37 % with a 25 % probability of survival at 1 year [6]. It is estimated that 22 % of patients with advanced cirrhosis have serum sodium levels $<$130 mEq/L; however in patients with refractory ascites or HRS, this proportion may increase to more than 50 % [7]. In the majority of patients, hyponatremia occurs in close association with an impairment of renal function and correlates with poor prognosis. Recent studies also indicate that hyponatremia is an important marker of prognosis in patients with cirrhosis awaiting liver transplantation and may be associated with an increased morbidity, particularly neurological complications, and

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reduced survival after transplantation [8–11]. In addition a number of studies have also demonstrated that the incorporation of serum sodium can improve the predictive accuracy of the Model for End-Stage liver disease (MELD) score in patients listed for liver transplantation [12–14].

Types of Hyponatremia

Patients with cirrhosis may develop either hypervolemic or hypovolemic hyponatremia. Hypervolemic or dilutional hyponatremia, is by far the most common type that occurs in patients with cirrhosis and it occurs in the setting of an expanded extracellular fluid and plasma volume. Hypervolemic hyponatremia in cirrhosis is due to a marked impairment in the renal capacity to eliminate solute-free water leading to disproportionate water retention with respect to sodium retention. It may occur spontaneously or as a consequence of excessive hypotonic fluids (for example, by giving an undue amount of iv hypotonic fluids—5 % dextrose—during a hospitalization) or other complications of cirrhosis such as in the setting of some bacterial infections [15]. By contrast, hypovolemic hyponatremia is less common and is due to significant losses of extracellular fluid, particularly from the kidney due to overdiuresis from diuretic treatment or from gastrointestinal tract. Hypovolemic hyponatremia is characterized by a reduction of plasma volume, lack of ascites and/or edema, signs and dehydration, and prerenal renal failure. Most patients with hypovolemic hyponatremia show an improvement of serum sodium levels after the administration of normal saline or by increasing sodium content in the diet temporarily. In this chapter we will focus on the pathogenesis and treatment of hypervolemic hyponatremia.

Pathogenesis

The pathogenesis of increased solute-free water retention in cirrhosis is intricate and involves several factors, including high levels of arginine vasopressin (AVP), reduced synthesis of renal prostaglandins, and reduced delivery of filtrate to the ascending limb of the loop of Henle [1, 3, 4]. Among these, AVP is the most important factor in the pathogenesis of water retention in patients with cirrhosis and ascites [16]. In cirrhosis, splanchnic vasodilation leads to arterial underfilling which unloads high-pressure baroreceptors that stimulate a non-osmotic hypersecretion of AVP leading to solute-free water retention and hyponatremia (Fig. 8.1) [16]. The physiological actions of AVP are exerted through three types of receptors present in target cells throughout the body [17]. These receptors are G protein-coupled receptors known as V1a, V1b, and V2 receptors. V1a and V1b are associated to the phosphoinositol signaling pathway with intracellular calcium as second messenger. V1a is responsible for vascular smooth muscle cell contraction,

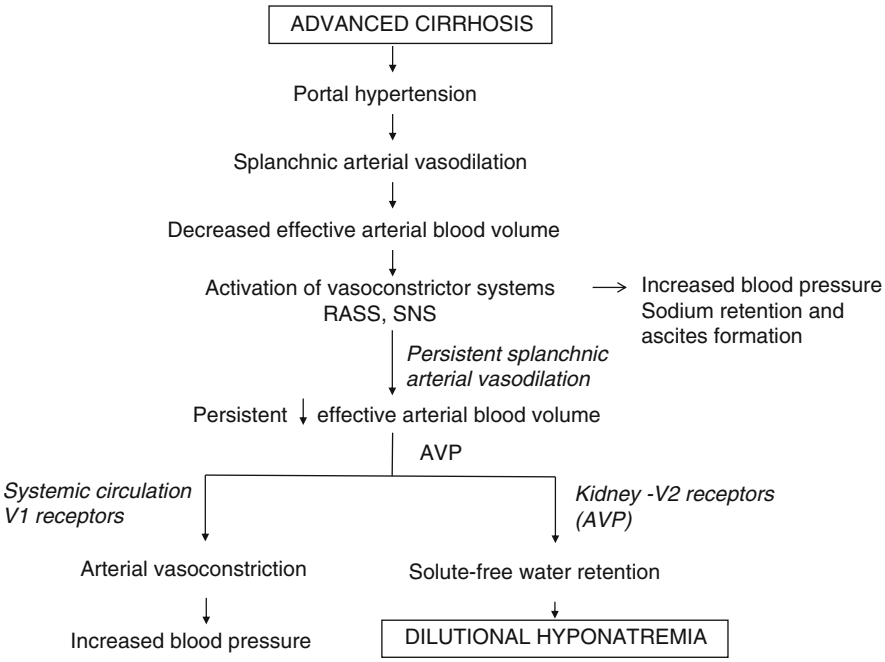

Fig. 8.1 Proposed pathogenesis of hypervolemic hyponatremia in cirrhosis. There is activation of the renin–angiotensin–aldosterone system (RAAS) and sympathetic nervous system (SNS) and a non-osmotic hypersecretion of arginine vasopressin (AVP) due to decreased effective arterial blood volume that activates baroreceptors and stimulates the hypothalamic release of AVP causing renal solute-free water retention through the action of V2 receptors and arterial vasoconstriction through the action of V1 receptors

platelet aggregation, and hepatic glycogenolysis and V1b is expressed in the anterior pituitary where it intervenes in adrenocorticotropin release [17].

The V2 receptors are located on the basolateral (capillary) membrane of the principal cells of the kidney collecting ducts and are responsible for the AVP-induced solute-free water reabsorption [3, 16, 17]. The effect of AVP in the kidney collecting duct occurs by means of specific water channels called aquaporins (AQP). The most important one in solute-free water retention is AQP2. This water channel has been characterized in human and rat kidneys and is expressed almost exclusively in the principal cells of the collecting ducts [18, 19]. The binding of AVP to the V2 receptor stimulates adenyl cyclase via the stimulatory G protein and promotes the formation of cyclic AMP (cAMP). This cAMP binds to a regulatory subunit of protein kinase A, which in turn phosphorylates AQP2, which is then translocated from vesicular bodies present in the cytosol to the luminal (apical) plasma membrane of the collecting duct cells and acts as a water channel thereby increasing water permeability [3]. The water entering the cell by the luminal plasma membrane leaves the cell through the basolateral membrane and enters the capillaries in contact with the tubular cells. Data from patients with

cirrhosis and hypervolemic hyponatremia in whom V2 receptor antagonists of AVP (vaptans) were administered indicate that hypersecretion of AVP plays a major role in the development of hyponatremia because these drugs induced an increase in serum sodium concentration in a large proportion (60–70 %) of patients [20]. However, there are a number of patients in whom serum sodium levels do not increase with vaptans which suggests that other mechansims involved in solute-free water retetion play an important role in the pathogenesis of hypervolemic hyponatremia in cirrhosis.

Clinical Features

There is not a lot of information on the clinical consequences of hypervolemic hyponatremia in cirrhosis. This is because hyponatremia occurs in the setting of advanced liver failure and patients may present with a range of nonspecific symptoms attributed to their underlying cirrhosis. Therefore, the precise recognition of specific clinical consequences due to hyponatremia in cirrhosis has not been possible. This has been further flawed by the lack of effective treatments for hyponatremia.

Neurological Features

In patients without liver disease, hyponatremia is primarily associated with a wide range of neurological manifestations related to the existence of brain edema, such as headache, confusion, focal neurological deficits, seizures, and, in some cases, death due to cerebral herniation [2]. The severity of neurological symptoms in patients with hyponatremia without liver disease correlates with the levels of osmolality and sodium in the extracellular fluid. Nevertheless, rather than the absolute reduction in serum sodium levels, the most important factor in determining the severity of neurological symptoms is the rate of fall in serum sodium levels [2]. Patients with acute hyponatremia have a much higher incidence of neurological symptoms than those with chronic hyponatremia.

There are no studies that have specifically evaluated neurological symptoms in patients with cirrhosis and hyponatremia. However, clinical experience indicates that neurological manifestations such as headache, focal deficits, seizures, and cerebral herniation are very uncommon. It is likely that the relatively low incidence of neurological manifestations in patients with cirrhosis and dilutional hyponatremia is related to the fact that most of these patients have chronic hyponatremia, and this gives sufficient time for brain adaptation to hypoosmolality. In most patients with cirrhosis, hyponatremia is asymptomatic, but some data indicate that hyponatremia is associated with a higher risk of hepatic encephalopathy [21–23]. The mechanism by which hyponatremia is associated with hepatic encephalopathy is likely due to changes in

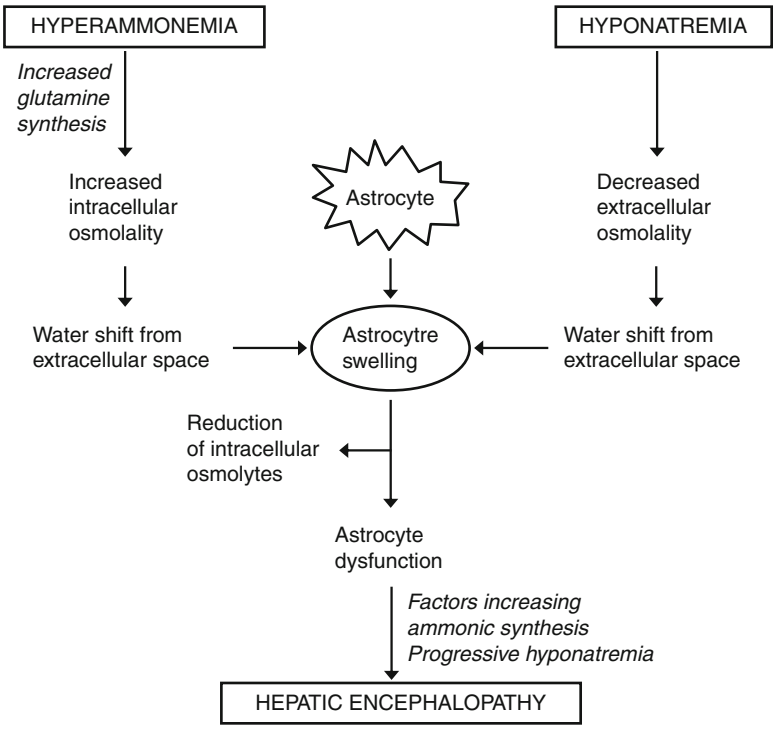

Fig. 8.2 Proposed interaction between hyperammonemia and hyponatremia on brain astrocytes and possible pathogenic relationship with hepatic encephalopathy. Reproduced from reference [4] with permission from John Wiley & Sons, Inc.

serum osmolality that lead to astrocyte swelling and then cellular release of solutes as a response to prevent cell swelling and cerebral edema (Fig. 8.2). These changes are relevant because the underlying pathogenesis of hepatic encephalopathy in cirrhosis is felt to be based on the fact that ammonia and other toxins induce a low-grade cerebral edema due to astrocyte swelling secondary to increased intracellular levels of glutamine that alter astrocyte function [24]. Consequences of astrocyte swelling include alterations in gene expression and oxidative stress that alter glioneuronal communication and disturb neurological function, leading to encephalopathy [24, 25]. Thus the presence of hyponatremia in combination with hyperammonemia, by favoring astrocyte swelling, may increase the risk of hepatic encephalopathy.

Complications of Cirrhosis

Aside from hepatic encephalopathy, hyponatremia is also associated with other complications of cirrhosis, yet information is limited. Hyponatremia is a frequent finding in patients with cirrhosis and bacterial infections. In the majority of patients,

hyponatremia occurs in close association with renal failure and correlates with poor prognosis [15, 26]. Moreover, it is important to note that patients with ascites and hyponatremia constitute a population with a very high risk of developing hepatorenal syndrome [27]. On the other hand, low serum sodium levels are a very common finding in patients with hepatorenal syndrome.

Information on the impact of hyponatremia on health-related quality of life in patients both with and without liver disease is limited. In patients with cirrhosis, hyponatremia impairs quality of life because patients require a restriction of daily fluid intake to prevent further reductions in serum sodium concentration, and this is usually poorly tolerated. Moreover, in a recent study in a large population of patients with cirrhosis and ascites, hyponatremia was an independent predictive factor of the impaired health-related quality of life [28].

Management of Hyponatremia

The first step in the management of hyponatremia in cirrhosis is to identify whether hyponatremia is hypovolemic or hypervolemic, because the management is completely different according to the type of hyponatremia. Diuretic treatment should be stopped in all patients, because diuretics may reduce serum sodium levels [5]. The management of hypovolemic hyponatremia consists on the identification and treatment of the cause of sodium loss together with the administration of sodium (either regular saline i.v. or diet with normal sodium content) [5].

A key aspect in the management of hypervolemic hyponatremia is to increase renal solute-free water excretion with the aim of reducing the increased total body water. The advantages of treating hypervolemic hyponatremia in cirrhosis are the following: (1) the reversal of hyponatremia may allow to avoid fluid restriction, (2) since hyponatremia has been shown to be a predisposing factor to hepatic encephalopathy, the improvement of serum sodium concentration may help reduce the risk of encephalopathy and (3) in patients awaiting liver transplantation, the normalization of serum sodium concentration before transplantation may reduce the risk of neurological complications after transplantation. The available therapeutic methods for the management of hypervolemic hyponatremia are summarized below.

Fluid and Water Restriction

Fluid restriction is still considered the first step in the management of hypervolemic hyponatremia [5]. There are no studies specifically assessing the effectiveness of fluid restriction in this setting; but in some cases it is helpful in preventing a

progressive decrease in serum sodium levels. Clinical experience indicates that it rarely increases serum sodium concentration in a significant manner. This lack of efficacy is likely due to the fact that in practice total daily fluid intake cannot be restricted to less than 1 L per day, an amount that is generally insufficient to cause a markedly negative fluid balance.

Sodium Chloride

The use of intravenous hypertonic sodium chloride in cirrhosis has not been investigated in randomized studies. Hypertonic sodium chloride has a very partial and short-lived effect in improving serum sodium concentration in cirrhosis perhaps because it has no effect on renal solute-free water excretion. Moreover, it has a major drawback; that is, increasing ascites and edema due to the severe sodium retention present in these patients because of the large amount of sodium given.

Albumin

Two short-term studies including a low number of patients suggest that the administration of albumin improves serum sodium concentration in patients with hypervolemic hyponatremia [29, 30]. This beneficial effect of albumin is probably related to an improvement in circulatory function with suppression of several sodium and water-retaining systems, including AVP. Although an attractive therapy, the effects were studied in only 1 week and the changes therefore short lived. The use of albumin for hyponatremia, although probably impractical due to the need of daily intravenous administration, could be further investigated in a subset of patients that would benefit from a short-term therapy (i.e., patients with very advanced liver disease awaiting liver transplantation). Further studies in larger series of patients and for prolonged periods of time are needed to assess the potential benefits of albumin administration on hypervolemic hyponatremia in cirrhosis.

AVP Antagonists: The Vaptans

The pharmacological approach to treatment of hypervolemic hyponatremia was revamped with the introduction of vaptans. These drugs are active orally and cause a selective blockade of the V2-receptors of AVP in the principal cells of the collecting ducts [31]. In healthy subjects, the administration of vaptans induces a marked and dose-dependent increase in urine volume with low urine osmolality due

Table 8.1 Short-term clinical studies using V2 receptor antagonists in patients with cirrhosis and ascites and hyponatremia

Author (ref)	Compound	Dose	Phase	Patients	Efficacy/side effects
Wong [32]	Lixivaptan[a]	50–500 mg/day po	II	44[b] treated for 7 days	Increased urine output, CH_2O, S osm, SNa. Dehydration with doses of 500 mg. Drop-out rate—27 %
Gerbes [33]	Lixivaptan[a]	100–200 mg/day po	II	60 treated for 7 days	Increased SNa, decreased U osm and body weight. Thirst appeared in patients at the 200 mg dose
Ginès [35]	Satavaptan[a]	5 mg, 12.5 mg, and 25 mg daily	II	110 treated for 14 days	Concomitant spironolactone 100 mg/day. SNa increased to ≥135 mEq/L or>5 mEq/L in 50–80 % of cases
Cardenas [36]	Tolvaptan[a]	15 mg increased to 30 mg and 60 mg as needed	III	63 treated for 30 days	Significant increase in AUC for SNa in tolvaptan group. Normalization of sodium levels (>135 mEq/L) occurred in 30 % of subjects after 1 month

U osm urinary osmolality, *S osm* serum osmolality, CH_2O solute-free water clearance, *SNa* Serum sodium, *U vol* urine volume, *AUC* area under the curve
[a]Randomized, double-blind, placebo-controlled trial
[b]Included five patients with cardiac disease and five with SIADH

to a marked increase in solute-free water excretion, but without an increase in urinary sodium excretion. Randomized, double-blind, comparative studies indicate that treatment with vaptans for a short period of time (up to 1 month), including tolvaptan, lixivaptan, and satavaptan, improves serum sodium concentration in patients with cirrhosis and hypervolemic hyponatremia [32–36]. A small study suggests that intravenous conivaptan, a vaptan that is not only an antagonist of the V2 receptors but also of the V1 receptors of AVP, is also effective in patients with cirrhosis and hyponatremia [37]. The increase in serum sodium concentration occurs within the first 7 days of treatment and normalization of serum sodium concentration has been observed in up to 80 % of patients [32–36] (Table 8.1). Moreover, in approximately one-third of additional patients, serum sodium increases more than 5 mEq/L but does not reach values >130 mEq/L. Therefore, vaptans are effective in the short-term treatment of hypervolemic hyponatremia in patients with cirrhosis.

It should be mentioned that treatment with vaptans has been assessed for the management of ascites in cirrhosis. Specifically, satavaptan was evaluated for the treatment of ascites in association with diuretics with the rationale that by increasing diuresis the vaptan would help manage ascites and prevent its recurrence. Although results of phase-2 studies were promising [38], phase-3 long-term treatment studies in three different populations of patients with cirrhosis and ascites demonstrated a

lack of efficacy in both, ascites management and prevention of its recurrence [39]. Moreover, use of satavaptan was associated with an increased mortality in one of the studies but not in the other two and the drug was withdrawn from development. The reason for this increased mortality could not be elucidated. It is not known if this increased mortality during long-term treatment is a class effect or is exclusively related to satavaptan. A small study in 18 patients with cirrhosis and ascites without hyponatremia showed that the administration of tolvaptan dose dependently decreased body weight and improved ascites and edema, however the results of this observation needs to be further studied in large cohorts of patients before considering this agent a treatment for patients with ascites [40].

The most frequent side-effect reported in studies evaluating the vaptans in patients with hyponatremia is thirst, which is related to the pharmacodynamic actions of these drugs. Potential theoretical concerns of the administration of vaptans in patients with cirrhosis are dehydration and hypernatremia and renal failure due to depletion of the intravascular volume. In short-term studies, hypernatremia (serum sodium >145 mmol/l) occurred in only 2–4 % of patients with cirrhosis treated with vaptans [32–36]. Nevertheless, the frequency of this complication may be higher if patients are treated with high doses of vaptans. An important concern is to avoid a rapid increase in serum sodium that could lead to neurological complications due to osmotic demyelination syndrome. In double-blind studies, an increase greater than 8 mEq/L per day within the first days of therapy has been reported with low and similar frequency in patients treated with vaptans compared to patients treated with placebo, ranging from 4 to 14 % in different studies [32–34]. More importantly, osmotic demyelination syndrome has not been reported. It should be noted, however, that in all studies patients were treated in the hospital for the first 2 days of therapy, had free access to water, and followed strict protocols with daily measurement of serum sodium during the first days of therapy and temporary interruption of drug administration in patients in whom serum sodium increased more than 8 mEq/L per day. In short-term studies, no significant impairment of renal and circulatory function was found in vaptan-treated groups compared to placebo [35, 36]. Nonetheless, it should be pointed out that in these studies patients were treated for short periods of time, under strict clinical and analytical surveillance, and with low doses of diuretics. Therefore, it is not known whether the frequency of renal impairment could be higher under different conditions. Finally, vaptans are metabolized by CYP3A enzymes in the liver; therefore drugs or substances that are strong inhibitors of CYP3A such as ketoconazole, grapefruit juice, and clarythromycin among others, increase the exposure to vaptans and may be associated with larger increases in serum sodium concentration. By contrast, drugs that are inducers of the CYP3A system, such as rifampicin, barbiturates, and phenytoin, may decrease the effectiveness of vaptans.

The only vaptans currently approved for clinical use are tolvaptan, conivaptan, and mozavaptan. Tolvaptan is approved in USA for the management of severe (<125 mEq/L) hypervolemic hyponatremia and in Europe for the management of

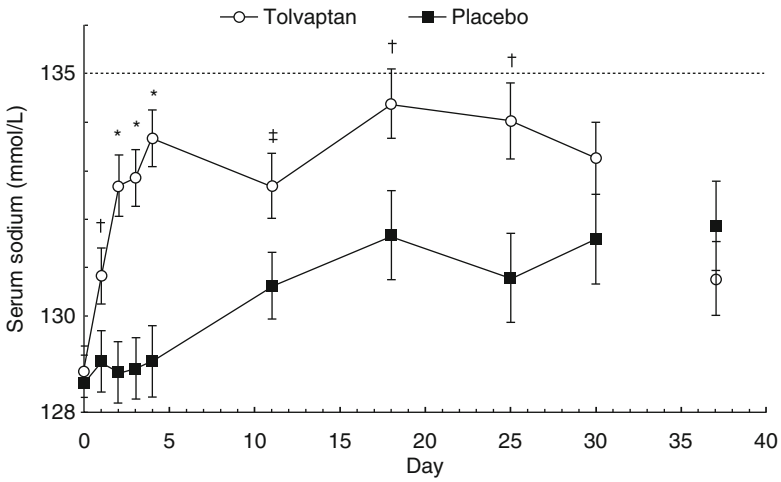

Fig. 8.3 Observed serum sodium concentration in patients with hyponatremia that received tolvaptan or placebo for 30 days and 7 days after stopping (day 37) Error bars are ± SE. *$P < 0.001$, tolvaptan vs. placebo; †$P < 0.01$, tolvaptan vs. placebo; ‡$P < 0.05$, tolvaptan vs. placebo. Reproduced from reference [36] with permission from Elsevier

SIADH. Conivaptan is also approved in the USA for the short-term (5-day) intravenous treatment of hypervolemic hyponatremia. Treatment of tolvaptan is started with 15 mg/day and titrated progressively to 30 and 60 mg/day, if needed, according to the desired changes in serum sodium concentration. The safety and efficacy of tolvaptan has only been reported for a short-treatment period (30 days) and the results indicate that mean serum sodium levels increased during the first 7 days and were maintained above 130 mEq/L during 30 days and levels dropped after the medication was discontinued (Fig. 8.3) [36]. In addtion, tolvaptan improved health-related quality of life in patients with cirrhosis and hypervolemic hyponatremia [36]. Very limited information exists on the effects of tolvaptan on serum sodium concentration for longer periods of time [41]. In randomized studies, a slightly increased frequency of gastrointestinal bleeding was reported in patients with cirrhosis and hyponatremia receiving tolvaptan compared to that in patients treated with placebo. This would require evaluation in future studies. Thus, studies assessing the efficacy and safety of long-term treatment with tolvaptan in patients with cirrhosis and hyponatremia are needed. On the basis of available evidence, the recommendations for the management of hypervolemic hyponatremia in cirrhosis are summarized in Table 8.2. Candidate patients to treatment with vaptans are patients with severe hyponatremia (<125 mEq/L) awaiting transplantation. Use of vaptans in patients not candidates to transplantation should be individualized in each case.

Table 8.2 Recommendations for the management of hypervolemic hyponatremia in cirrhosis

1. Fluid restriction up to 1,000–1,500 ml/day if hyponatremia persists despite diuretic withdrawal
2. If fluid restriction is not effective, oral tolvaptan may be used[a]. Intravenous conivaptan is an option but there is very limited data on its use in cirrhosis[b]
3. Tolvaptan treatment should be started in the hospital at a starting dose of 15 mg/day. This dose should be given for the first few days and then the dose should be titrated (to 30 and 60 mg/day) to achieve a slow increase in serum sodium concentration. Serum sodium concentration should be monitored closely particularly during the first days of treatment and whenever the dose of the drug is increased
4. Rapid increases in serum sodium concentration (of greater than 8 mEq/L per day) should be avoided to prevent the potential occurrence of osmotic demyelination syndrome. If serum sodium increases over 8 mEq/L, the administration of tolvaptan should be interrupted transiently
5. Neither fluid restriction nor administration of saline should be used in combination with vaptans to avoid a too rapid increase in serum sodium concentration
6. Patients may be discharged after serum sodium levels are stable and no further increase in the dose of the drug is required
7. Treatment with drugs that are either potent inhibitors or inducers of the CYP3A should be avoided
8. The duration of treatment with tolvaptan is not known. Safety has only been established for short-term treatment (one month). Withdrawal of tolvaptan is associated with recurrence of hyponatremia in most patients

[a]Tolvaptan is approved in the USA for patients with cirrhosis with severe hyponatremia (serum sodium $\leq$125 mEq/L) as well as for other conditions with hypervolemic hyponatremia. In Europe, tolvaptan is only approved for the syndrome of inappropriate antidiuretic hormone secretion
[b]Conivaptan is only available in the USA

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Chapter 9
Hyponatremia in Psychosis

Pichai Ittasakul and Morris B. Goldman

Introduction

Despite the clinical significance of the water imbalance in psychiatric patients and the effective interventions that are available, hyponatremia is frequently undetected. Hence, its recognition and proper management are an important and neglected aspect of patient care. Chronic and often mild hyponatremia is seen in a range of psychiatric disorders and is typically a consequence of medication-induced impairments in water excretion, which may or may not be compounded by primary polydipsia. It causes an array of neurologic and medical problems similar to those seen in nonpsychiatric patients. More acute, episodic water intoxication has caused many deaths in those with severe mental illness. Episodic water intoxication is a consequence of a marked primary polydipsia and transient impairments in water excretion that frequently coincide with psychotic exacerbations. While primary polydipsia, per se, occurs across psychiatric disorders, intermittent hyponatremia and episodes of water intoxication occur almost exclusively in patients with severe mental illness and are attributable to resetting of the osmostat for AVP release. In this chapter, we review the clinical presentation, sequelae, epidemiology, pathophysiology, diagnosis, and treatment of intermittent hyponatremia and episodic water intoxication in those with severe mental illness, and more briefly review hyponatremia secondary to psychotropic medications.

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Historical Overview of Hyponatremia as a Clinical Problem in Psychiatry

Since the 1930s, unexplained (1) increases in water intake [1], (2) impairments in water excretion which vary with severity of psychosis [2], and (3) reports of water intoxication [3] have been linked to chronic psychotic disease. In the following decades, hyponatremia was often unnoticed and patients were frequently thought to have a primary seizure disorder [4]. In the 1950s, 1960s, and 1970s, the emergence of biological psychiatry, the characterization of the syndrome of inappropriate antidiuretic hormone secretion (SIADH), the increased interest in distinguishing diabetes insipidus from primary polydipsia, and finally the development of a sensitive assay for arginine vasopressin (AVP) all contributed to a renewed interest in disorders of water balance in psychiatric patients [5, 6].

Initial efforts to characterize the water imbalance were obscured by the different etiologies of the hyponatremia as well as the complexities of antidiuretic function [7]. Thus, the early studies did not distinguish patients with idiopathic hyponatremia from those with iatrogenic hyponatremia (typically attributable to thiazide diuretics, carbamazepine, or antidepressants) or other recognized causes like hypothyroidism or severe alcoholism [8, 9]. Unlike these recognized causes, idiopathic hyponatremia was always associated with marked polydipsia and minor impairments in water excretion [10]. Indeed, there were cases in which the diluting capacity appeared normal, and others where the diluting defect was transient [7]. Most cases of water intoxication were therefore attributed to polydipsia alone ("self-induced water intoxication") and when impaired excretion was found it was frequently attributed to sequelae of hyponatremia (e.g., nausea, seizures) [9]. This view was altered, although not eliminated, when Hariprasad et al. in 1980 demonstrated reset osmostat in schizophrenia patients with idiopathic hyponatremia [11]. To distinguish these patients from those with hyponatremia due to recognized factors, Vieweg coined the term "psychosis, intermittent hyponatremia, polydipsia" (PIP) syndrome [12].

Clinical Presentation and Sequelae of Hyponatremia in PIP Patients

PIP patients usually have a severe unrelenting psychosis [13]. Polydipsia typically appears about 5 years after the onset of the psychiatric illness, and hyponatremia appears about 5 years after that [12], though rarely water intoxication occurs concurrently with the first psychotic break [14]. Patients often hide their drinking, and symptomatic hyponatremia may be suspected only after someone notes a striking diuresis in a post-ictal patient. Because the impairment in water excretion is relatively minor, water accumulates over the course of the day and is excreted at night. Thus the hyponatremia is most marked in the mid-afternoon and is frequently

not present if blood samples are only obtained in the morning. This pattern of drinking and of water retention have led to some unique clinical observations: institutionalized PIP patients in the winter tend to congregate at midday around heaters (so-called afternoon radiator sitting syndrome) [15].

Signs and symptoms of acute hyponatremia are dependent on the severity and rapidity of its development [16]. Generally, the clinical presentation of symptomatic hyponatremia resembles that of nonpsychiatric patients [17, 18], but may include aggravation of the underlying psychiatric illness (e.g., increased paranoia and aggression). Nausea, vomiting, and ataxia commonly precede frank water intoxication, but conversely patients may appear normal one moment and begin seizing the next. Frank neurological symptoms (e.g., lethargy, seizures, coma) usually do not occur until serum sodium concentration falls below 120 mEq/L or even lower in those with chronic hyponatremia [19]. Hyponatremia in PIP patients as well as in medication-induced cases may present with rhabdomyolysis or compartment syndrome [20, 21]. Antipsychotic-induced hyponatremia has frequently been reported to co-occur with neuroleptic malignant syndrome [22].

Mild to moderate hyponatremia (i.e., 125 mEq/L) often appears to be asymptomatic [23], but most of these patients have impaired cognition, characterized by deficits in attention, learning, memory, and executive function which may be difficult to distinguish from the underlying mental illness [18, 24]. These patients are also at greater risk of falls and fractures [25–27]. Chronic polydipsia per se is also associated with morbidity, including pathologic fractures [28] and bladder dysfunction that can lead to renal failure [29].

Epidemiology

Psychiatric disorders in general are associated with a higher risk of hyponatremia. The increased risk is primarily attributable to the elevated frequency of primary polydipsia and the prescribing of medications which impair water excretion [30–36], as well as the PIP syndrome summarized above (Table 9.1) [18, 35]. Carbamazepine, thiazide diuretics, and antidepressants are the most commonly identified medications. Many psychotropic medications induce transient nausea and orthostatic hypotension, (i.e., AVP stimuli), but these are not routinely implicated in hyponatremia in this population. The incidence of primary polydipsia in chronically psychotic patients is 15–25 %, and about one in five of these experiences intermittent hyponatremia (i.e., PIP syndrome) [37–39]. The incidence of medication-induced hyponatremia in polydipsic psychotic patients is not clearly established, but is likely about the same or higher based on population surveys [37, 40]. The incidence of primary polydipsia in nonpsychotic patients varies between about 2 and 10 % depending on the disorder. In rare cases, hyponatremia likely occurs from primary polydipsia alone (i.e., “self-induced”), though this has never been (and would be difficult to) conclusively demonstrate.

Table 9.1 Risk factor for hyponatremia in psychiatric patients

Primary polydipsia
Increasing age
Heavy smoking
Alcoholism
Polypharmacy
Chronic psychosis
Drugs (e.g., use of diuretic, SSRI, TCA, venlafaxine, bupropion, carbamazepine, and calcium antagonist)
Medical conditions that decrease water excretion (e.g., kidney diseases, Syndrome of inappropriate antidiuresis, heart failure, hypothyroidism, adrenal insufficiency)

SSRI selective serotonin reuptake inhibitor, *TCA* tricyclic antidepressants

Other reported risk factors associated with hyponatremia (Table 9.1) are smoking, which is a recognized stimulus for AVP release and has been shown to contribute to impaired water excretion in case reports [41]. Smoking is extremely common in schizophrenia patients (~70 %), especially in the hyponatremic subset [38]. This also places patients at increased risk of SIADH associated with small cell lung cancer. Alcoholism is also common in psychiatric patients and the associated malnutrition or cirrhosis in severe cases can predispose polydipsic patients to hyponatremia. Furthermore, alcoholism is independently associated with polydipsia in PIP patients [12, 42]. Finally, polypharmacy, per se, appears to be a risk, though this may simply be additive effects of two or more medications associated with impaired water excretion [43].

Over the past 30 years there have been many reports of deaths in severely mentally ill patients due to water intoxication [44, 45]. Hawken et al. [46] recently examined the long-term effects of polydipsia and hyponatremia on mortality. The median age at death was 57 years for hyponatremic polydipsic, 60 years for normonatremic polydipsic, and 68 years for matched non-polydipsic schizophrenia patients. Hyponatremic patients had a 74 % greater chance of dying before non-polydipsic patients.

PIP patients and their first-degree relatives differ from others with schizophrenia [42, 47–49]. PIP patients are more severely debilitated by the mental illness and exhibit an increased incidence of primary sensory deficits [50]. Further study is needed to determine if these patients have a distinct subtype of severe mental illness.

Pathophysiology

Mechanism of Impaired Water Excretion

Several groups have shown that the impaired water excretion in PIP patients is attributable to reset osmostat [11, 51–53]. In addition, these patients exhibit enhanced renal sensitivity to low levels of AVP [51, 54]. The resetting varies over time,

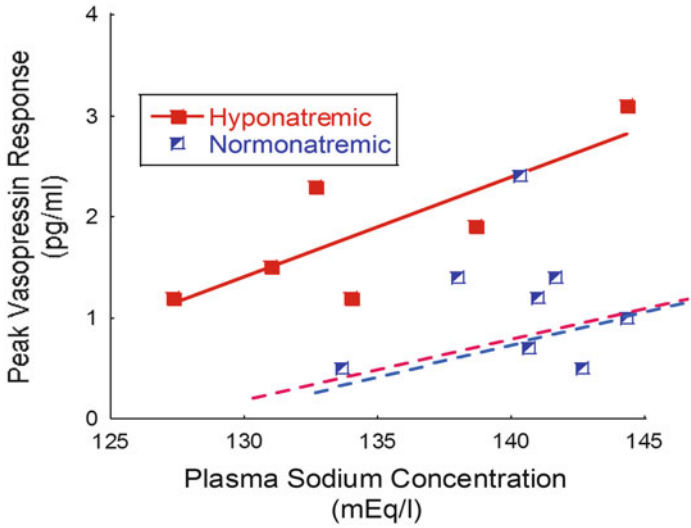

Fig. 9.1 AVP secretion following induced psychosis in PIP patients. The figure shows peak AVP levels in polydipsic hyponatremic patients (PIP) and polydipsic normonatremic patients following a psychotomimetic. Both groups exhibited a transient increase in psychosis, and the AVP response was predicted by basal positive psychotic symptoms. AVP rose more in the PIP patients despite their lower plasma sodium levels. The figure also shows that peak responses in PIP patients were proportional to their concurrent plasma sodium levels (*solid red line*; $df = 7, r = 0.80, P = 0.05$). Extrapolation of the line suggests the set point for AVP declined to a level capable of inducing water intoxication (~110 mEq/L). *Dotted red* and *blue lines* show the mean relationship between AVP and plasma sodium in the two groups following a water load and hypertonic saline infusion administered 2 weeks prior to the psychotomimetic (see Ref. [50]). Note the set point for AVP release at that time appeared to be about 130 mEq/L

appearing to normalize with habituation to the research setting and to worsen during psychotic exacerbations [55] (Fig. 9.1). Neither the enhanced secretion nor the enhanced action of AVP can be explained by recognized factors and thus conform to Type C and Type D SIADH, respectively. The two findings, together with the patients' polydipsia can produce moderate hyponatremia (e.g., 125 mEq/L), but are generally not severe enough to produce water intoxication [51]. Water intoxication can occur, however, following acute psychosis which drops the AVP set point to about 110 mEq/L [56]. The effect of psychosis on the set point also cannot be attributed to recognized factors.

Several investigators initially attributed the variation in the AVP set point to acute stress [7]; however, stress does not increase AVP unless recognized AVP stimuli are induced. The discovery that the anterior hippocampus normally restrains AVP and stress hormone responses to psychological stress [57, 58] and that this hippocampal segment is smaller in PIP patients [59, 60] led to the hypothesis that hippocampal pathology might induce an enhanced AVP response to stress in PIP patients. This hypothesis has been supported by subsequent studies. One demonstrated that both AVP and stress hormone responses to a psychological, but

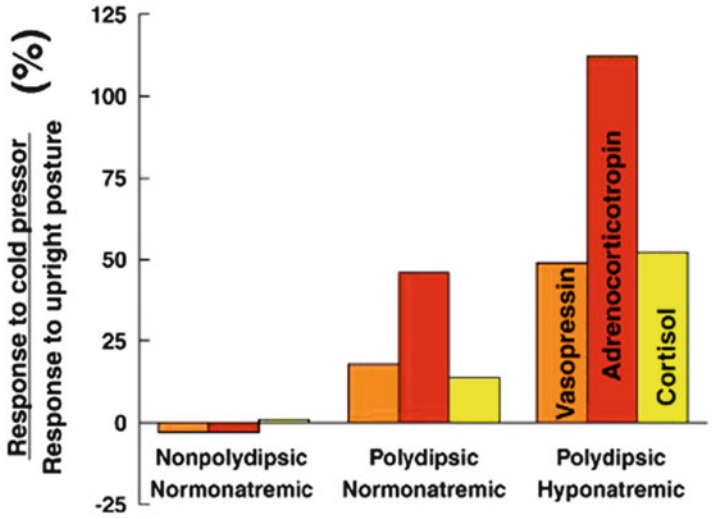

Fig. 9.2 Ratio of peak plasma vasopressin, adrenocorticotropin, and cortisol responses to a 60-s immersion in ice water (cold pressor) and a postural stimulus in nonpolydipsic normonatremic, polydipsic normonatremic, and polydipsic hyponatremic schizophrenic (PHS) patients. Responses of healthy normals (not shown) generally resemble those of the polydipsic normonatremics. The hippocampal formation is thought to normally constrain neuroendocrine responses to the cold pressor as it (unlike the postural stimulus) is determined by emotional factors. Thus the findings support the view that hippocampal-mediated responses to psychological stress are enhanced in PHS but blunted in patients without water imbalance. (Adapted from Goldman, 2009, with permission from Elsevier) [55]

not a physical (postural), stimulus were enhanced in PIP patients relative to healthy controls and nonpolydipsic schizophrenics [61]. The AVP response to the psychological stressor was predicted by concurrent plasma osmolality and thus consistent with lowering of the AVP set point. A second study showed that hippocampal-mediated negative feedback, which contributes to braking the stress response, was nearly absent in PIP patients [62] (Fig. 9.2). A third study showed these neuroendocrine findings were proportional to deformations on the surface of the hippocampus overlying the segment (anterior lateral) which projects to the anterior hypothalamus and normally restrains neuroendocrine release [63] (Fig. 9.3). Together these findings support the conclusion that hippocampal pathology in PIP patients produces symptomatic hyponatremia and water intoxication by disrupting the restraint of neuroendocrine responses to psychological stress.

The hippocampal findings summarized above are also proportional to deformations on the amygdala and anterior hypothalamus [63], two structures, like the hippocampus, that modulate both neuroendocrine activity to stress and are implicated in the pathophysiology of schizophrenia. In particular, the same hippocampal region that restrains these neuroendocrine responses also restrains dopamine release in the ventral striatum (which many believe underlies acute psychosis and behavioral response to stress [64]). Integrity of the anterior lateral hippocampus also appears necessary for coping efforts to buffer the impact of stress [65]. Together these findings support the hypothesis that the neuroendocrine dysfunction is part of a

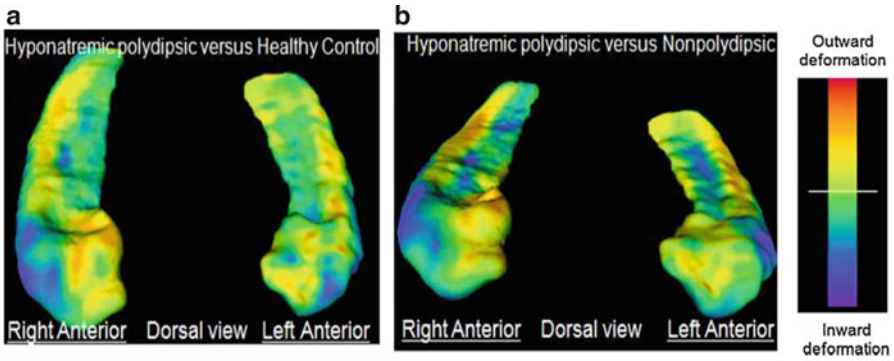

Fig. 9.3 Hippocampal shape differences showing statistically significant ($P < 0.05$: surface point-wise, without multiple comparison correction) deformations in the surface maps of PHS compared to healthy controls (*panel* **a**) and PHS compared to nonpolydipsic patients (*panel* **b**) Note the inward deformations on the bilateral anterior lateral surfaces in PHS (**a** and **b**: *blue*) and on the right anterior medial surface in NNS (**b**: *orange*). (Adapted from Goldman et al., 2011, with permission from Elsevier) [63]

general increased vulnerability to psychological stress in these patients, thus potentially linking the impaired water excretion to the underlying mental disorder.

Unlike the transient changes in the set point for AVP secretion, little is known about the mechanism of the enhanced renal sensitivity to AVP action and its relationship to the altered AVP secretion. While antipsychotics may contribute to the finding, they cannot account for it [66]. Polydipsia, per se, does not appear to be responsible, although the possibility there is an idiosyncratic response (perhaps due to longstanding polydipsia) in PIP patients has not been excluded. One obvious target that has not been explored is the integrity of V2 receptor function, per se.

Mechanism of Polydipsia and Relationship to Reset Osmostat

The osmotic set point for desiring water, like that for AVP, appears to be reset downward in polydipsic patients with and without hyponatremia [54], consistent with the view that their thirst regulation is generally intact but pathologically altered by an extrinsic factor [51, 54]. Whether the set point drops further during acute psychosis or acute stress is not known [56]. The relative increase in desire for water does not seem attributable to increased thirst or to hydrophilic delusions [67, 68]. When asked most patients say they drink because drinking makes them feel better [69, 70].

The hippocampal dysfunction previously described in these patients could contribute to polydipsia as hippocampal lesions enhance the development of polydipsia and stereotypic behaviors in stressed animals [71]. Polydipsic patients also exhibit an increased incidence of stereotypic behaviors compared to others with schizophrenia [72, 73]. To date, however, there has been no clear evidence linking the polydipsia to hippocampal dysfunction. One other unexamined possibility is that

the hippocampal dysfunction enhances the rewarding properties of water, since the projections from the hippocampus to the striatum also modulate reward [64].

Diagnosis

Because hyponatremia in PIP patients is intermittent and most apparent in the afternoon, morning (i.e., routine) serum sodium levels cannot be relied on to make the diagnosis [12]. Even if the set point for AVP is reset downward, morning serum sodium levels may be near normal because of a concurrent concentrating defect attributable to "medullary washout" from the polydipsia [54]. The amount of retained water required to induce dilutional hyponatremia is significant and because accumulation begins again each morning, patients at risk of water intoxication can be easily identified by obtaining diurnal measures of body weight. Acute water intoxication is commonly associated with a marked increase in body weight (i.e., 20 % decrease in plasma sodium typically is accompanied by a 8-kg increase in body weight in the typical 70 kg person) [12], but on a typical day these patients gain only 2–3 kg. Thus determining the difference between morning and afternoon body weights is a reliable means of diagnosing the PIP syndrome. The diagnosis of hyponatremia can be confirmed by obtaining a plasma sodium along with the afternoon weight.

Concurrent urine samples may or may not identify a diluting defect as reset osmostat is difficult to confirm unless serial measures of plasma sodium and urine osmolality samples are obtained following water loading. Urine may be maximally and appropriately dilute (e.g., $<$ 60 mOsm/Kg) depending on how far below the AVP set point current plasma sodium has fallen. This is particularly likely to be the case following an acute episode of water intoxication. If the patient is only mildly hyponatremic (e.g., 128–132 mEq/L) urine osmolality may be low (typically between 100 and 250 mOsm/Kg) but still reflect the antidiuretic effects of low levels of AVP. Urine may not rise much above this level, even when the patient is normonatremic because of the concurrent diluting defect. While it has not been clinically used for this purpose, the rapid resolution of hyponatremia after a single dose of an AVP antagonist (~8 h) may be a simple way to confirm the presence of enhanced AVP secretion or action [74].

Differential Diagnosis

Medication-induced hyponatremia is particularly common in psychiatric patients, especially in the elderly and those with primary polydipsia. Serotonin reuptake inhibitors (SSRIs) are commonly implicated, having a risk about four times higher than that of other antidepressants [30, 75]. Elderly women during the first few weeks of therapy appear to be at the highest risk [75]. It appears likely that any antidepressant which enhances serotonin activity (e.g., trazodone, chlomipramine) may increase the risk of hyponatremia, though reports appear to have occurred with

all agents including mirtazapine and bupropion [30–34, 36]. Other serotinergic agents, including street drugs such as methylenedioxymethamphetamine (MDMA: ecstasy), have also been associated with hyponatremia, perhaps by directly enhancing vasopressin secretion [76].

Medication-induced hyponatremia is typically more stable than that seen in PIP patients, because of the more limited role of polydipsia and the more severe impairment in water excretion (i.e., urine osmolality > plasma osmolality). For these reasons, a single concurrent measure of urine and plasma osmolality are likely adequate to make the diagnosis. Depending on the half-life of the compound (the half life of the SSRI, fluoxetine, is 2–7 days), these cases should rapidly resolve with discontinuation of the responsible agent. In the absence of a rapid reversal then the other factors noted in Table 9.1 should be considered.

The Role of Antipsychotics in Hyponatremia

The role of antipsychotic medication in hyponatremia remains controversial. There are convincing case reports showing rapid reversal of hyponatremia when antipsychotic medication is discontinued, and recurrence with rechallenge [77–80]. However, this must be balanced with evidence that (a) impaired water excretion predates antipsychotic medications [2]; (b) antipsychotics do not generally increase AVP levels and indeed normalize elevated levels in some with acute psychosis [79]; (c) dose reduction does not improve hyponatremia [81]; and (d) lower, not higher, doses are more likely to be associated with hyponatremia [22]. While antipsychotics may modestly enhance renal sensitivity to AVP in a dose-related manner, this effect does not appear to contribute to the hyponatremia [54, 82]. These data are consistent with the view that antipsychotic medication does not contribute to the impaired water excretion in most psychotic patients and is more likely to ameliorate hyponatremia in the typical PIP patient.

The mechanism of antipsychotic-induced hyponatremia is unknown but rarely involves recognized stimuli (nausea, hypotension). Like other drug-induced cases, antipsychotic-induced hyponatremia is more stable than that seen in PIP patients and is attributable to severe impairments in water excretion that can usually be confirmed with a concurrent urine and plasma osmolality samples. Furthermore, antipsychotic-induced hyponatremia is often confounded by other clinical issues like neuroleptic malignant syndrome, rhabdomyolysis, or lung cancer [22].

Treatment and Prevention

This section addresses treatment and prevention for PIP patients, as treatment for other psychiatric patients with hyponatremia resembles that of the general medical patient.

Acute Symptomatic Hyponatremia in PIP Patients

Following an acute episode of water intoxication, the appropriate response to most PIP patients is close observation and fluid restriction. This conservative approach is influenced by the relatively minor contribution of the impairment in water excretion, the rapid shifts in fluid balance, as well as an increased risk of overcorrection due to the concurrent concentrating defect. Thus, patients who have seized and have regained consciousness or who are exhibiting symptoms of impending water intoxication (tremors, ataxia, vomiting) can be fluid restricted for 3–4 h during which is time they will excrete large amounts of the retained water. Patients must be closely monitored as they may continue to absorb ingested water from their gastrointestinal tract and (re)develop water intoxication. Monitoring changes in body weight are an effective means of assessing the efficacy of fluid restriction [12]. Prolonged fluid restriction or infusion with normal or hypertonic saline is unnecessary and should generally be avoided because of the concentrating defect and subsequent risk of overcorrection. However, evidence suggests that rapid correction per se is safe [10] as long as the patient is not alcoholic and overcorrection is avoided [83]. The risk of developing central pontine myelinolysis in PIP patients is likely mitigated by the lack of adaptation of the patient to any specific sodium level [10]. Following resolution of the acute episode one of the preventive measures discussed below should be considered. Should the patient not rapidly regain consciousness or should a marked diuresis not occur, standard measures of restoring water balance (e.g., hypertonic saline infusion) should be considered and other etiologies for the hyponatremia explored.

Prevention

Targeted fluid restrictions are an effective means of preventing water intoxication in the inpatient or nursing home setting and enable the patient and nursing staff to avoid the intensity of constant monitoring [12, 84]. The procedure relies on the fact that water retention leads to easily detected gains in body weight, and the "target weight" is based on an estimate of the weight gain at which the patient's hyponatremia is more severe than usual but not yet at a level likely to induce water intoxication. The procedure requires weighing patients twice a day (morning and afternoon) and whenever latent signs of water intoxication are observed. Initially the target can be set at 7–10 lbs above the patient's morning water weight and a sodium level obtained when this target is exceeded (although this is not strictly required). If the target is too conservative, it can be increased to a level closer to that associated with symptomatic hyponatremia. Thus, it may take a few days to find a target weight that conforms to a sodium level that warrants fluid restriction. Fluid restrictions of 2–6 h are usually sufficient to return the patient to their morning weight.

Pharmacologic Treatment

Until the introduction of clozapine and the vaptans, the pharmacologic options were very limited. While many agents had been tested, none, except perhaps for demeclocyline, appeared even minimally effective [68].

Clozapine

Many investigators have reported that clozapine reduces the risk of hyponatremia and water intoxication [85], though there have been no double-blind placebo controlled studies. The mechanism is unclear, but clozapine may lower water intake rather than enhance water excretion. The drug often normalizes sodium levels within several weeks enabling patients to leave restricted settings and participate in therapeutic programming. Clozapine may be effective in very low doses (approximately 100 mg/day), and there is no evidence that going above 300 mg/day will produce further improvements in water balance [85]. Water intoxication and other sequelae of polydipsia have, however, occurred in patients on clozapine [86]. Plus, clozapine requires monitoring that is not available to all physicians, and clozapine can cause an impressive array of life-threatening adverse effects. Thus the risk benefit ratio needs to be weighed, particularly in those patients with mild hyponatremia who do not experience episodic water intoxication.

Vaptans

A double-blind study documented the marked efficacy of tolvaptan (Samsca), a competitive vasopressin receptor 2 antagonist in PIP [74]. Nineteen PIP subjects were randomly assigned to receive placebo ($n = 12$) or tolvaptan ($n = 7$) once daily for 30 days at a dose of 15–60 mg, based on serum sodium changes. Basal levels were 130 mEq/L in both groups and normalized (>135 mEq/L) within 24 h of treatment in those receiving tolvaptan but did not change in those on placebo. The salutary effects were apparent throughout the 30-day treatment period, and subjects on tolvaptan returned to previous hyponatremic levels after the treatment was stopped. Two subjects receiving active drug (28.6 %) became dehydrated and experienced hypotension, and five subjects receiving placebo (41.7 %) experienced symptoms associated with dilutional hyponatremia. The study also included an open-label extension arm in which the salutary effects appeared to be maintained (Goldman, Josiassen; unpublished data). As of this writing, these medications in the USA are limited to acute inpatient settings, but presumably at some point will become integrated into routine outpatient care. Careful dose adjustment will be needed to prevent dehydration, particularly in patients with concurrent medical problems (e.g., renal insufficiency).

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Chapter 10
Exercise-Associated Hyponatremia

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Introduction

Hyponatremia is the most common electrolyte disorder seen in nursing home and hospitalized patients [1]. However, in the past few decades it has also been described in athletes of both genders who participate in prolonged endurance events [2–5]. The term exercise-associated hyponatremia (EAH) has been used to describe hyponatremia developing in endurance athletes who participate in events lasting greater than four hours, and is clinically defined as a serum sodium concentration <135 mEq/L occurring up to 24 h after prolonged exertion [6]. Based on the symptoms associated with hyponatremia, an athlete with EAH can present in two forms: (1) athletes with isolated serum sodium levels <135 mmol/L who are either asymptomatic or have mild nonspecific symptoms such as nausea and (2) those presenting with confusion, seizures, and altered mental status, in association with serum sodium levels <135 mmol/L, who are considered to have exercise-associated hyponatremic encephalopathy (EAHE). EAHE is a potentially life-threatening condition. Although, EAH and especially EAHE are considered relatively rare occurrences in endurance athletes, it is becoming an increasingly more common

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finding in all ultra-endurance (>6 h) events worldwide, and is now well recognized as a cause of event-related fatality [6, 7]. Rapid diagnosis of EAH and the more severe form EAHE are critical to ensure good outcomes.

Much debate occurred in the late 1980s into the early 1990s regarding the possible etiology of EAH. Two camps emerged: one that supported overconsumption of water (dilutional hyponatremia) as the prime etiology [8] and the other supported excessive body sodium loss as the driving force [9]. Data are now most consistent with excess fluid consumption being the most important pathogenic feature with a smaller, variable component of solute loss [4–6].

EAH was first reported in the 1981 Comrades ultradistance marathon foot race between Pietermaritzburg and Durban, South Africa [8]. One case included a 46-year-old woman who developed EAH symptoms at approximately 70 km of the 90-km event [10]. After being driven to the medical tent at the finish line, she was administered 2 L of fluids for presumed dehydration. Since her symptoms continued to deteriorate she was transported in a vehicle back to Durban and while en route she suffered a grand mal seizure and lapsed into a coma. On admission to a hospital she was reported to have serum sodium of 115 mEq/L. She was diagnosed with EAHE with neurogenic (noncardiac) pulmonary edema secondary to overhydration of fluids.

In the following year, Frizzell et al. [11] described the development of EAH in a physician and medical student running in an ultramarathon in Chicago, USA, 1983. Both runners consumed over 20 L of fluid within 8–10 h and were diagnosed with EAH. Each patient was managed differently (3 % saline vs. 0.9 % saline) resulting in one being discharged within 8 h (3 % saline) and the other remaining semi-comatose for 36 h.

The emergence of EAH case presentations in the early to mid-1980s can be explained by the fact that endurance athletes were initially advised up to the late 1960s to avoid drinking fluids and consuming sodium during exercise since it was believed that it was not essential [12]. This paradigm shifted with the publication of an influential article by Wyndham and Strydom [13], which suggested that inadequate fluid consumption during marathon running was detrimental to performance. This in turn resulted in the development of hydration guidelines with the prevailing advice to have athletes consume the maximal amount of fluid that can be tolerated during exercise [5]. This dictum to consume as much fluids as tolerated during prolonged endurance events has likely influenced the greater emergence of EAH cases and deaths.

Since these case presentations by Noakes [8] and Frizzell [11], there have been many other EAH/EAHE published case presentations, prospective and retrospective research studies and review articles, two international EAH consensus reports, and other educational venues all in effort to educate clinical providers in both prehospital and in-hospital settings, and athletes and coaches about the causes, treatment, and prevention strategies for EAH/EAHE [4–7]. The objective of this chapter is to present the current consensus and findings for EAH/EAHE incidence rates, risk factors, pathophysiology, clinical management guidelines, and prevention strategies.

Epidemiology

The incidence of asymptomatic and symptomatic cases of EAH varies widely with regard to the geographical location of the event, type and duration of activity, gender, and ambient temperature during the event. Cases of "asymptomatic" hyponatremia are largely detected via convenient samples taken from consenting athletes participating in research screening protocols. Asymptomatic cases of EAH generally represent those which meet the biochemical diagnostic criteria for hyponatremia (blood sodium concentration <135 mmol/L) and are of unknown clinical significance. Obviously, the incidence of asymptomatic EAH is greater than the incidence of "symptomatic" EAH, which generally refers to a biochemical diagnosis of EAH combined with debilitating symptomatology, most often including significant mental status changes and perhaps pulmonary edema as well (EAHE).

Epidemiology of Asymptomatic EAH

The highest reported incidence of "asymptomatic" hyponatremia has been noted in ultramarathon races covering 161 km (100 miles) in North America, where the incidence of EAH has ranged between 30 and 51 % [14–16]. Two of the 161-km footraces recording the highest number of hyponatremic finishers were conducted in peak temperatures of ~37 °C [14, 15], while the other 161-km race with a 44 % incidence of EAH was conducted in temperatures ranging between −8 and 4 °C [16]. Conversely, similar ultradistance marathon races have reported no cases of EAH at equally high ambient temperatures [17] or at greater racing distances (181 km) [18]. Thus, the seemingly logical presumption that the incidence of hyponatremia increases over distance and time and at higher ambient temperatures is difficult to support.

Other endurance events have variable reported levels of EAH. For example, the incidence of biochemical EAH in Ironman Triathlons has been reported to be as high as 18 % [19] to 25 % [20] while negligible in another [21]. Studies on endurance cyclists have yielded a range in incidence of EAH from no cases in a 720-km race completed in a mean time of 28.9 h [22] to 12 % in cyclists participating in a 109-km road race (mean racing time ~5 h) [23]. Seventeen percent of 36 swimmers participating in a 26.4-km swim (average finish time ~9 h) developed asymptomatic hyponatremia in a race where individual race crews provided food and fluid to each athlete throughout the swim [24]. At the standard marathon distance (42.2 km), 12–13 % of race finishers were diagnosed with asymptomatic EAH from the 2003 London [25] and 2002 Boston Marathons [26]. The range of reported incidences has been between zero [27] and 28 % [28] at the standard marathon distance.

Collectively, in the largest cohort analysis of 2,135 athletes participating in eight endurance events, the incidence of biochemical EAH was 6 % [10]. The ambient temperature range of reported cases varied between the extremes of −8 °C [16] and 37.6 °C [14]. With regard to gender, the majority of studies document a higher incidence of EAH in females versus males. For example, in the Boston Marathon study of 488 race finishers, 22 % of females and 8 % of males developed EAH [26]. In 330 New Zealand Ironman Triathletes, 45 % of female and 14 % of male race finishers were diagnosed with EAH [19]. Although the incidence of EAH is substantially higher in females, it is important to recognize that males are not "spared" from developing EAH.

Epidemiology of Symptomatic EAH (EAHE)

Cases of symptomatic EAH are generally reported as isolated cases presenting to medical facilities (medical tents at races and hospitals) for treatment related to a spectrum of symptoms ranging from feeling unwell to collapse with seizure activity. However, a few separate criteria have been utilized to evaluate the potential for clinical severity in the two largest cohorts analyzed to date. More specifically, in a large cohort analysis of 2,135 athletes, "clinically significant" hyponatremia was defined as a cutoff serum sodium concentration of <128.9 mmol/L [10]. According to this definition, the overall incidence was 1 % although it was unclear if the entire cluster of athletes reported significant symptoms [10]. Similarly, in 488 Boston Marathon finishers, 0.6 % developed "critical hyponatremia" represented by a serum sodium concentration below 120 mmol/L [26]. This small percentage of race finishers, however, did not appear symptomatic for EAH at the time of testing [26]. Other than these two reports, the reporting of symptomatic clusters of EAH detailed below represent small numbers of athletes seeking medical attention.

The majority of reported cases of symptomatic hyponatremia were in runners or in events where running was the last event (Ironman Triathlon). Nine confirmed deaths of public record have been directly attributed to complications associated with EAHE [25, 29–31]. The overall incidence of symptomatic EAH in all marathon participants is generally below 1 % [31, 32], but the percentage of EAH seen in all symptomatic athletes seeking medical care has been reported to be as high as 23 % in an Ironman Triathlon [19] and 38 % in runners participating in a marathon and ultramarathon in Asia [33]. The most alarming epidemiological trend is that symptomatic EAH is now being reported in shorter distance events such as a half marathon [34] and sprint distance triathlon taking 1 h and 33 min to complete [35].

Also at the turn of the second millennium, symptomatic cases of hyponatremia were being reported with increased frequency in both hikers and military personnel. The reported incidence of hyponatremia in Grand Canyon hikers seeking medical care from exercise-associated collapse or exhaustion from May 31, 1993 through September 31, 1993 was 16 % with an estimated incidence rate between 0.02 and 0.4 per 1,000 persons [36, 37]. In the United States Military, between 1989 and

1999 there were 190 hospitalized cases of hyponatremia [38]. Data from the Defense Medical Surveillance system, however, estimated an incidence rate between 0.01 and 0.03 per 1,000 person years across all military populations from 1997 to 2005 [37]. There have been four reported deaths from hyponatremia in the military [39, 40]. Thus, although less strenuous than running, even very modest hiking and marching activities in young and healthy individuals [41] have led to documented morbidity and mortality from EAHE.

More unusual presentations associated with more modest exercise levels have been reported in: a football player presenting to the trainer's room with cramps and receiving 8 L of hypotonic fluid [42] and a 48-year-old male lawn bowler, heterozygous for the Delta F508 cystic fibrosis mutation, bowling in 42 °C heat [43]. Cases of symptomatic EAH have also been induced in two separate laboratory studies involving low intensity exercise conducted in high (>30 °C) ambient conditions [44, 45]. Deaths from hyponatremia have also been reported in the lay press in a 25-year-old male police officer participating in a 12-mile bicycle training ride [46], a 17-year-old male football player after a summer practice [47], and in a case of fraternity hazing involving a 21-year-old male pledge performing calisthenics in a cold cellar [48]. Many more of these unfortunate events have likely occurred and either have not been recognized or reported on.

In summary, the incidence of asymptomatic hyponatremia ranges from 0 to 51 % while cases of symptomatic hyponatremia are much lower (<0.5 % of all standard marathon runners). However, at least nine deaths from EAHE have been reported in the literature, five females and four males. The incidence of asymptomatic cases of EAH which eventually progress to life-threatening EAHE is currently unknown and requires further investigation.

Risk Factors for EAH

Case series of athletes who have developed EAH reveal that the development of EAH is associated with identifiable risk factors, some of which may be modifiable. The major risk factor for EAH is a high rate and total amount of fluid intake during and immediately after exercise [11, 21, 26, 31, 32, 49]. For example, in the Boston Marathon, the development of EAH was independently associated with weight gain during the race (which could only occur from fluid intake) and the amount of weight gained correlated with the severity of hyponatremia (17 % of runners who gained at least 2.0 kg developed hyponatremia) [26]. In a large review of 2,135 athletes participating in endurance races, the authors estimated that athletes who gained more than 4 % body weight during exercise had an 85 % probability of developing hyponatremia [10]. Of note, not all athletes who develop EAH gain weight during exercise suggesting that while excessive consumption of fluids is a clear risk for the development of EAH, it is not absolutely required [14, 15]. However, severe hyponatremia is rare in athletes who lose weight during the event [31]. It is also important to note that consumption of sports beverages, which typically contain

carbohydrates and electrolytes, do not provide protection against the development of EAH [26, 31]. This is due to the fact that these drinks are hypotonic to plasma and that the typical sodium plus potassium content is approximately 20–30 meq/L.

Other risk factors for the development of EAH include: longer race times, female gender, slower training pace, and a low body mass index [21, 26, 31, 32, 49]. While some studies have implicated the use of nonsteroidal antiinflammatory agents (NSAIDS) as a risk factor for EAH [50], others have not [26]. Conceptually, NSAIDS could increase the risk for EAH due to their ability to increase the activity of arginine vasopressin (AVP) by removing the inhibitory effect of prostaglandins. The role of other medications that can lead to non-osmotic secretion of AVP such as selective serotonin release inhibitors has not been studied in this group.

Pathogenesis of EAH

The two major pathogenic mechanisms that account for the development of EAH are: (1) increased fluid intake and (2) impaired urinary water excretion due largely to persistent secretion of AVP [4, 5].

As noted above, increased fluid intake appears to be the primary risk factor for the development of EAH. This is reflected in the weight gain seen in the majority of athletes who become hyponatremic. However, a source of "endogenous" water that may contribute to the increase in extracellular water in athletes who develop EAH is derived from the breakdown of glycogen during exercise [51]. Water is found in a complex with glycogen in the liver and muscle, and as glycogen is metabolized, water is released without a concomitant weight gain. How much this mechanism contributes to the risk of EAH without weight gain is not known.

Individuals with normal renal function, ingesting a regular diet, can excrete between 500 and 1,000 ml/h of water [52]. With the additional, non-renal losses of water due to sweat and insensible fluid losses, athletes should be able to consume as much as 1,000–1,500 ml/h before developing water retention and hyponatremia. Thus, while fluid ingestion is necessary to develop EAH, it is likely not sufficient except in those circumstances where water intake is very excessive (>1,500 ml/h).

Failure to suppress AVP can markedly reduce the ability of the kidneys to excrete a water load. For instance, in normal circumstances, ingestion of water should suppress AVP leading to production of dilute, high volume urine (urine osmolality as low as 50 mOsm/kg and a volume of 500–1,000 ml/h). If AVP is not suppressed appropriately with water loading, then the ability to produce dilute urine is markedly impaired (for instance, low level persistence of AVP can result in a fixed urine osmolality of 150 mOsm/kg and a decrease in the rate of water excretion by two-thirds as compared to a urine osmolality of 50 mOsm/kg). In fact, the available data support the concept that many athletes who develop EAH have submaximal suppression of AVP and an inappropriately high urine osmolality [30]. This is similar to the syndrome of inappropriate antidiuretic hormone secretion (SIADH). There are a number of non-osmotic stimuli that lead to secretion of

AVP that may be operable in endurance athletes: intense exercise itself; nausea and/or vomiting; hypoglycemia; and nonspecific stresses such as pain and emotion [23, 53, 54]. Not all AVP release in athletes may be inappropriate as excessive sweat sodium losses may induce volume depletion and appropriate secretion of AVP. This appropriate AVP secretion may be important in those athletes who develop EAH along with net weight loss.

While the combination of excessive water intake along with inappropriate AVP secretion will clearly lead to hyponatremia, other factors may be operable in endurance athletes. Suggesting that other factors may be operative, was the important finding that in the review of 2,135 athletes, 70 % of the athletes who gained weight during the event maintained normal serum sodium levels [10]. What explains this finding as well as the fact that some athletes may lose weight and become hyponatremic?

In a study of endurance athletes running for a mean of 6 h and ad libitum fluid intake, it was noted that despite a mean 3.8 kg mass loss, serum sodium was maintained at normal levels [55]. While, not surprisingly, AVP levels were elevated, so were the levels of brain natriuretic peptide (NT-BNP) despite the loss in plasma volume [55]. The elevations in BNP may lead to excessive losses of urine sodium and raise the risk of hyponatremia. Further studies are needed in order to determine how much urine solute loss may contribute to the development of EAH.

A possible mechanism for maintenance of a normal serum sodium level despite weight gain is the release of sodium from internal stores [10]. Up to 25 % of body sodium is bound in bone (to negatively charged proteoglycan matrix) and though not osmotically active is potentially recruitable into an osmotically active form [56, 57]. Thus, this pool could minimize the fall in serum sodium induced by overhydration. This may explain the following findings, which were reported in 18 athletes who were hospitalized for EAH [10]. Sodium and water balance were estimated at the time of admission and measured during recovery. At the time of admission, the predicted serum sodium based upon electrolyte and water balance estimates was higher than the actual concentration in 14 of the 18 athletes. This suggested exchange of sodium from an osmotically active to an inactive state and worsening of the hyponatremia. Interestingly, during recovery, 8 of the athletes showed evidence of osmotic activation of sodium (the increase in serum sodium was greater than could be explained by simple balance of sodium and water intake and output). On the other hand, 10 of the athletes showed evidence of osmotic inactivation of sodium (the increase in sodium was less than could be explained by simple balance of sodium and water intake and output).

There are other factors likely operative in endurance athletes that affect the serum sodium. However, their impact on the development of EAH is speculative [4, 5]. These include: (1) the absorption of water retained in the gastrointestinal tract at the end of the race which will lower the serum sodium; (2) the breakdown of glycogen into smaller, more osmotically active molecules, such as lactate, during exercise which will initially increase cellular osmolality and shift water into cells leading to a rise in serum sodium, and then reverse within 5 min after the cessation of exercise and lower the serum sodium [58, 59], and (3) changes in potassium

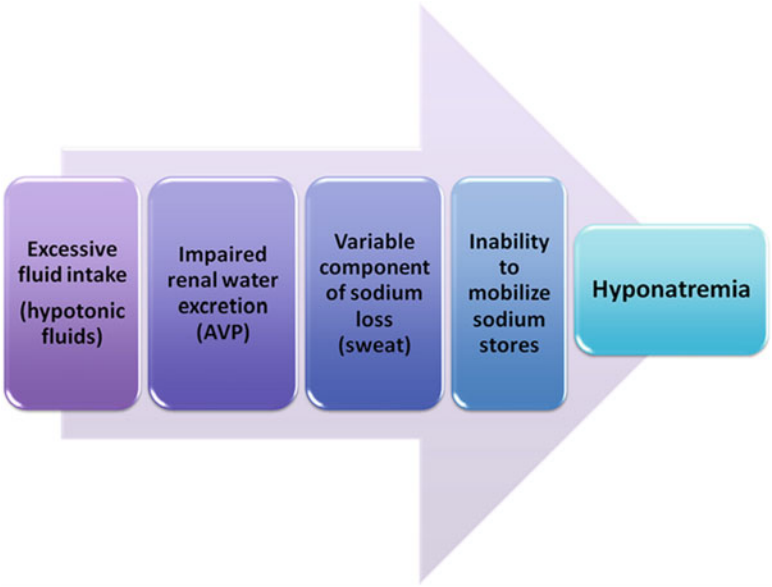

Fig. 10.1 Major pathogenic features that ultimately lead to exercise-associated hyponatremia

balance that serve as effective osmoles and affect the serum sodium such that hypokalemia will lead to hyponatremia.

The issue of whether sweat sodium loss contributes to the development of EAH remains controversial. There is a highly variable degree of sodium loss from sweat (ranging from 15 to 65 meq/L) and as compared to the general population endurance athletes generally have lower sweat sodium levels [60, 61]. The direct effect of losing hypotonic sweat would be to raise the serum sodium. However, sweat loss could contribute to the development of hyponatremia if the degree of fluid loss were sufficient to produce significant volume depletion and provide a stimulus to AVP release and thereby, impair urine excretion of water. In this case, there would also have to be ingestion of hypotonic fluids. This scenario may explain the finding of EAH developing in some athletes with net weight loss [14, 15]. However, sweat solute loss is likely only a minor contributing factor, as one study documented that the mean sodium deficit of athletes with EAH was only 104 meq [10]. This observation is consistent with another report in which the plasma volume was maintained in 181 triathletes despite a mean mass loss of 4.9 kg during the race [62].

Thus, the pathogenesis of EAH is complex (Fig. 10.1) with the two main factors being the excessive ingestion of water and inappropriate secretion of AVP. There are likely numerous variations on this theme, which reflect variable contributions from other mechanisms such as sweat sodium loss, osmotic inactivation of sodium, and variable potassium losses.

Treatment of Exercise-Associated Hyponatremia

Historical Perspective

Early clues to the appropriate management of EAH came with the previously referenced paper published by Frizzell and co-workers describing two participants of the 1983 American Medical Joggers Association 50-mile and 100-km ultramarathons [11]. At the time of the event, race guidelines advised runners to drink 300–350 ml per aid station which amounted to 15–18 L in the 50-mile event and 18–22 L in the 100-km event. The second place finisher of the 100-km event was a 24-year-old medical student who was reported to have become "stuporous and disoriented" within 5 min of finishing. He was found to have a serum sodium concentration of 123 mmol/L. After treatment with intravenous (IV) normal saline, he developed seizures and was semicomatose for 36 h. Fortunately, he ultimately recovered and was discharged in satisfactory condition on the fifth hospital day. In contrast, a 45-year-old physician who became "disoriented and confused" about 30 min after finishing the 50-mile event, and with a serum sodium of 118 mmol/L, was treated with IV 3 % hypertonic saline. He was fully alert in 3 h and was discharged after 8 h. Fluid intake was estimated at 20 L and 24 L for the 100-km and 50-mile runners, respectively. The authors cautioned about excessive fluid intake, commented that the postexercise onset of EAH symptoms might be due to accelerated gastric emptying with cessation of exercise, and noted the apparent benefit of hypertonic saline over normal saline in the treatment of EAH.

Since the report of these two cases, other case reports have provided additional support for the efficacy of IV hypertonic saline over normal saline in the treatment of EAH [29, 30, 32]. Furthermore, clinical trials during the 2009 and 2010 161-km Western States Endurance Run demonstrated that 100 ml of IV 3 % hypertonic saline in neurologically asymptomatic finishers with EAH resulted in a 2–4 mmol/L increase in serum sodium concentration within 60 min [63].

Additional work has focused on the potential of treating EAH with oral hypertonic saline. Siegel and colleagues describe treatment of three runners from the 2008 Boston Marathon with "mental status changes" and serum sodium concentrations of 128–133 mmol/L [64]. Each was tolerant of oral intake and was provided oral 9 % saline from concentrated broth (4 bouillon cubes in ~120 ml water). Each had rapid symptomatic recovery, and serum sodium concentrations reached normal levels within approximately 15–25 min.

At the 2009 and 2010 Western States Endurance Run, a comparison between 100 ml of 3 % hypertonic saline given orally vs. IV among neurologically asymptomatic finishers with EAH was performed. In the larger trial, there was a significant and comparable increase in serum sodium concentration of 2 mmol/L in both groups over the 60-min treatment period. A significant body mass loss due to diuresis was also evident from the treatment received by both groups. Therefore, at least among those with mild EAH who can tolerate oral intake, hypertonic saline taken orally appears to be a viable treatment option.

Making the Diagnosis

A requisite for correctly diagnosing EAH is that it must be routinely considered in the differential diagnosis of an individual presenting for medical attention during or shortly after exercise. In fact, EAH can easily be mistaken for dehydration if the diagnosis is not considered. Differentiation between dehydration and EAH is critical as provision of isotonic or hypotonic fluids is appropriate for the dehydrated athlete [65], whereas such treatment could be disastrous for an athlete with EAH.

The second international exercise-associated hyponatremia consensus development conference concluded that "medical directors should ensure the availability of on-site serum sodium concentration analysis [6]." When EAH is routinely considered in the differential diagnosis of a collapsed runner and point-of-care serum sodium concentration analysis is available, the field diagnosis of EAH becomes straightforward. However, the reality is that on-site analysis of serum sodium concentration is not widely available. Even relatively large and established organized endurance and ultra-endurance events often have no capacity for on-site blood analysis. For perspective, of the 556 ultramarathon competitions in North America in 2010 that had at least 20 finishers, the median event size was only 56 runners. Given the small size of so many of these competitions, few events can legitimately provide little more than "first aid/first responder" medical capabilities, and many of them have no medical coverage at all.

Other limitations to the viability of point-of-care blood analysis at endurance events include the high cost of the analyzer and the expense associated with operation. Furthermore, even when point-of-care blood analysis is available, it can be technically difficult for events that traverse remote areas to assure such testing is available at all sites where it might be needed. Temperature sensitivity of the analyzers can be another issue that interferes with on-site analysis [14, 15, 66].

The development of salivary osmolality [67] or tear osmolarity [56] analyzers have resulted in some attention for possible use in defining hydration status, but are not viable diagnostic tools for EAH. Ideally, an inexpensive portable serum sodium analyzer that requires only a drop of blood and is operational across a wide temperature range will eventually become available. Until then, the availability of on-site determination of serum sodium concentration is too high of a standard to be expected of most organized endurance and ultra-endurance events. As such, the consideration of alternative diagnostic means has been explored. Unfortunately, the possible signs and symptoms that have been reported to be present with EAH are quite similar to those present with heat illness or dehydration (Table 10.1). Even oliguria, which would be typical of the dehydrated state, is also commonly seen with EAH when AVP secretion is part of the pathophysiological mechanism leading to a highly concentrated, low volume urine output.

In some environments, those developing EAH have been shown to be more likely to lose less weight or to gain weight during the exercise compared with those not developing EAH [10]. Among 2,135 observations, Noakes et al. demonstrated an indirect relationship between post-event serum sodium concentration and weight

Table 10.1 Signs and symptoms of EAH and heat illness or dehydration

	EAH	Heat Illness or Dehydration
General		
Fatigue/weakness	Possible	Possible
Increased thirst	Possible	Likely
Temperature		
Normal	Possible	Possible
Elevated	Possible	Possible
Cardiovascular		
Tachycardia	Possible	Likely
Orthostasis	Possible	Likely
Gastrointestinal		
Nausea/vomiting	Possible	Possible
Neurological		
Headache/dizziness	Possible	Possible
Blurred vision	Possible	Possible
Confusion/disorientation	Possible	Possible
Obtundation	Possible	Possible
Seizure	Possible	Not likely
Coma	Possible	Possible
Respiratory		
Distress	Possible	Not present
Urine Output		
Oliguria	Possible	Likely
Diuresis	Possible	Not present

change such that those who gained weight or lost the least amount of weight generally had lower serum sodium concentrations than those who lost more weight [10]. In fact, of those with EAH, only 25 % had lost more than 3 % body weight, and among those with "clinically significant" EAH (serum sodium concentration <129 mmol/L), none had lost more than 3 % body weight. As such, within that population, it was unlikely for an athlete to have clinically significant EAH with a weight loss of 3 % or more.

Interestingly, some recent observations at four 161-km ultramarathon runs in northern California have been considerably different. From 430 observations, a direct relationship between post-event serum sodium concentration and weight change was seen such that those who lost weight were more likely to have lower serum sodium concentrations than those gaining weight during the event [15, 66]. It was also found that of those with EAH, 40 % had lost more than 3 % body weight, and when just considering those with "clinically significant" EAH, 31 % had lost more than 3 % body weight with some losing more than 5–8 %. The explanation for the different findings between this study and that of Noakes and colleagues is not clear but may be due to the events in this cohort generally being longer in duration and likely under higher ambient temperatures. Nonetheless, in this environment, weight loss or gain has not proven to be helpful in making the diagnosis of EAH. This unfortunately means that the only reliable method of diagnosing EAH at present is through measurement of serum sodium concentration.

Field Treatment Guidelines

Perhaps the most important element in the treatment of EAH is to avoid exacerbating the condition with improper treatment. Pushing isotonic or hypotonic fluids, whether orally or intravenously, is contraindicated in EAH. It is also important to understand that serum sodium concentration does not necessarily correspond with the magnitude of symptoms. The necessary level of care and urgency in treatment is based upon symptoms.

Cases of mild EAH without neurological symptoms are likely to go unrecognized unless in a situation where post-event serum sodium concentration is being measured for another purpose. Those individuals with hyponatremia who are neurologically stable are best advised to limit fluid intake and consume salty snacks or a small volume of hypertonic fluid until the onset of urination. They should be observed for at least 60 min during the initial post-exercise period since water remaining in the gastrointestinal tract can be quickly absorbed at the cessation of exercise and result in rapid development of symptoms from EAH. They should also be advised to urgently seek medical attention if signs or symptoms of EAH develop.

Individuals with EAH who have neurological symptoms, regardless of the actual serum sodium concentration, should be treated emergently with hypertonic saline. When able to tolerate oral intake, a hypertonic solution of concentrated broth would be an appropriate initial treatment. If the individual is unable to tolerate oral intake, or when there is no improvement or symptoms worsen with oral hypertonic saline, the recommended treatment is a 100 ml bolus of 3 % hypertonic saline infused through a peripheral vein in <60 s [6, 7]. This can be repeated two additional times at 10 min intervals if not clinically improved. Experience has proven this treatment to be without untoward symptoms at the infusion site (no burning, phlebitis or residual discomfort). Supplemental oxygen, if available, should be provided to treat hypoxemia. The intent of the field management is to stabilize the subject until their care can be transferred to a definitive care medical facility. When transferring care, it is most important to relay the diagnosis of EAH and to caution the transport team about potential dangers of aggressive IV hydration with isotonic or hypotonic fluids.

The sodium load from each 100 ml bolus of 3 % hypertonic saline (51 mmol) is expected to increase serum sodium concentration by 1–2 mmol/L. There is evidence that such treatment also acts to expand the plasma volume which removes the volume-receptor stimulus for AVP secretion [63]. A reduction in AVP secretion should then cause an aquaresis which will result in an additional increase in serum sodium concentration. This increase in serum sodium concentration shifts the osmotic gradient and reverses neurological symptoms. Neurological improvement often occurs within minutes with minimal increase in serum sodium [64]. Furthermore, unlike the situation with rapid correction of chronic hyponatremia, there appears to be no risk of osmotic demyelination or central pontine myelinolysis with rapid reversal of EAH.

When the capacity for on-site serum sodium measurement is not available, the decision-making process becomes more challenging. Suspicion of EAH necessitates fluid restriction. Certainly in environments where the incidence of EAH is recognized to be high, such as certain ultramarathon runs where the incidence of EAH has been found to be as high as 30–51 % [14, 63, 66], one should resist treating athletes with IV normal saline without certainty that they do not have EAH. However, fluid restriction is contraindicated in the case of dehydration and rhabdomyolysis with impending acute kidney injury [65]. Thus, the lack of diagnostic capacity in the field creates a treatment dilemma. In the event of neurological deterioration without access to rapid determination of serum sodium concentration, the use of IV hypertonic saline, if available, is a consideration but, at present, cannot be recommended as being without potential risk. In some regard, one could make the argument that when point-of-care serum sodium concentration cannot be determined, it might be best to completely avoid the availability of IV supplies. Under such situations, an appropriate emergency transport system must be in place.

Additional considerations for endurance and ultra-endurance events that will not have on-site capabilities to measure serum sodium concentration include education of event participants about prevention of EAH and medical personnel about treatment guidelines for EAH. The unnecessary use of IV fluid replacement will also reduce the risk of exacerbating EAH. The assurance that an emergency transport system is in place becomes critical, and local emergency department physicians and transport personnel should also be educated about EAH.

Prevention

Prevention of exercise-associated hyponatremia is largely—if not exclusively—dependent on optimal fluid and sodium intake guidelines and drinking habits during exercise. Acknowledging the wide range of ambient temperature fluctuations during an athletic event, athlete size and experience level, exercise intensity and duration as well as individual stress levels, creation of a safe “one size fits all” range of pre-calculated fluid intake recommendations is an impossible task. Thus, more individualized strategies are necessary to accommodate all athletes participating in a wide variety of athletic endeavors.

In athletic events and exercise lasting less than 18 h, the predominant pathophysiological mechanism in the development of EAH is overconsumption of hypotonic fluids beyond the capacity to excrete any fluid excess [6]. There are two individualized strategies to prevent the overconsumption of fluid during exercise. The first strategy is to use body weight changes during exercise as a guide to estimate the amount of fluid lost during exercise, and rehydrate accordingly. This strategy is favorable to athletes desiring a more structured “pre-competition” hydration plan. However, this option of maintaining body weight during exercise should always be subservient to bodily cues suggestive of overhydration (bloating, gastrointestinal distress) [68]. Replacement of 100 % of body weight losses during

endurance races appear to result in overhydration due to the combination of substrate losses combined with the liberation of glycogen-bound water during exercise [10, 69]. Furthermore, although weight gain has been shown to be a reliable predictor of dilutional hyponatremia in athletic events lasting <18 h [10, 26], in athletic events lasting over 20 h, the reliance on body weight to predict hyponatremia is abolished or even inverted [15, 66]. Thus, estimations of body weight losses should be used as a guide rather than a rule, especially during uncontrolled settings (endurances races) where the potential for non-osmotic stimuli to AVP secretion (and water retention) are higher than in training.

The second, preferred, hydration strategy to prevent EAH is to drink according to the dictates of thirst [6]. Since the body strives to maintain plasma osmolality—not body weight—at rest and during exercise, drinking to thirst protects against dilutional hyponatremia without performance or health decrements [69]. Decreasing the number of fluid stations along a race course (optimal distance every 20 km in a cycle race and every 2.5 km in a marathon run) [70] and appropriate educational strategies designed to reverse inappropriate "drink as much as possible" beliefs and drinking behaviors [71] have also been shown to be effective in preventing the development of EAH.

Sodium supplementation during exercise has not been shown to be effective in the prevention of EAH during endurance exercise lasting <18 h. Sodium supplementation in athletes who lost >2 % body weight during an Ironman Triathlon did not affect serum sodium concentration [72, 73]. However, for athletes who hydrate to replace ≥100 % of body weight losses during exercise, sodium supplementation appears to attenuate the decline in serum sodium concentration but does not prevent the occurrence of hyponatremia if fluid intake exceeds fluid losses [68, 74]. It is important to note that most commercially available sports drinks are hypotonic to plasma, typically containing only 10–18 mmol/L of sodium, and do not offer a significant amount of supplemental sodium.

In summary, drinking according to the dictates of thirst before, during, and after exercise appears to be the primary strategy in preventing exercise-associated hyponatremia. Sodium supplementation may attenuate the decline in serum sodium concentration when fluid intake matches or exceeds body weight losses, but cannot prevent hyponatremia when sustained fluid intake exceeds fluid losses.

Summary

EAH is a potentially devastating condition that can complicate participation in endurance events. In recent years, a greater understanding of the risk factors and pathogenesis of EAH has led to a consensus recommendation regarding its treatment [6]. However, recognition of EAH and EAHE remains challenging and first responding medical personnel still require education in this regard. Ideally, on-site blood sodium measurement would be available at endurance events, but this is not practical. Thus, a high-index of suspicion is required in order to diagnose EAH.

Clearly, prevention is the key factor in protecting athletes and others from EAH. Unfortunately, there is no "one size fits all" recipe for fluid and salt consumption during endurance events, although drinking to thirst and avoiding water intakes $>$1,500 ml/h are prudent and reasonable recommendations. Education continues to be needed to ensure that athletes understand the risk of overdrinking and the consequences of EAH.

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Chapter 11
Vasopressin Receptor Antagonists

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Arginine Vasopressin: Physiology and Receptors

The nonapeptide arginine vasopressin (AVP), also known as antidiuretic hormone, regulates renal electrolyte-free water reabsorption primarily to maintain serum osmolality within a narrow physiologic range and secondarily to control blood volume and maintain systemic perfusion pressure [1]. The hormone is synthesized in the magnocellular neurosecretory cells located in the supraoptic and paraventricular nuclei of the hypothalamus and stored in the posterior pituitary. AVP is secreted in response to two main stimuli. The more sensitive stimulus is an increase in plasma tonicity. The less sensitive stimulus is a decrease in plasma volume, although the magnitude of the response to this stimulus is greater.

AVP receptors all belong to the rhodopsin-like, class-A, G-protein-coupled receptor family. The three receptor subtypes V1a, V2, and V1b differ in sites of expression, signal transduction mechanisms, and function (see Table 11.1) [2–4]. V1a receptors are coupled to a Gq/11 protein that is activated upon AVP binding. Activation of Gq/11 stimulates a signaling pathway involving phospholipase C, resulting in the release of intracellular calcium. The V1a receptor is widely distributed, and its effect is dependent on location. It is found predominantly on vascular smooth muscle, where it is associated with vasoconstriction and cardiac hypertrophy upon stimulation. The V1b receptor is found mainly in the anterior pituitary and is associated with adrenocorticotropin hormone and endorphin release, though its precise physiologic role has not been elucidated.

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Table 11.1 AVP receptor subtypes, location, function, and non-peptide antagonists

Receptor	Localization	Function	Non-peptide antagonist
V1a	Vascular smooth muscle	Vasoconstriction, myocardial hypertrophy	Conivaptan[a]
	Platelets	Aggregation	
	Hepatocytes	Glycogenolysis	
	Myometrium	Uterine contraction	
V2	Basolateral membrane of renal collecting duct	Insertion of AQP-2 channels into apical membrane, induction of AQP-2 synthesis	Mozavaptan Satavaptan Lixivaptan Conivaptan Tolvaptan
	Vascular endothelium	VWF and factor VIII release	
	Vascular smooth muscle	Vasodilation	
V1b	Corticotroph cells of the anterior pituitary	ACTH and beta-endorphin release	

[a]Dual V1a/V2 receptor antagonist
AQP-2 aquaporin-2; *VWF* von-Willebrand factor; *ACTH* adrenocorticotropin hormone

The V2 receptor is found predominantly in the principal cells of the renal collecting duct, as well as in vascular endothelium. In the former location, stimulation of this receptor results in the reabsorption of electrolyte-free water. The V2 receptor is coupled to a Gs protein which dissociates upon AVP binding. One of the dissociated subunits activates adenylyl cyclase. The resulting increase in intracellular cyclic 3′, 5′-adenosine monophosphate (cAMP) and activation of protein kinase A causes the exocytic insertion of preformed vesicles containing aquaporin-2 (AQP2) water channels into the apical membrane. This series of events increases water permeability in the collecting duct and facilitates reabsorption.

Historical Perspective on the Development of Vasopressin Receptor Antagonists

Arginine "vasopressin" was named based on the late nineteenth century finding by Oliver and Schaefer (1895) that pituitary gland extracts exhibited vasopressor activity when injected into the anesthetized dog [5]. Shortly afterwards, other investigators identified cells of the posterior lobe as being responsible for this effect. More than a decade later in 1913, the concomitant antidiuretic effect of the posterior pituitary was discovered independently by two different physicians: Farini in Italy and von den Veldon in Germany. Each successfully treated patients with diabetes insipidus by injecting them with posterior pituitary extracts.

In the early 1950s, AVP was isolated and synthesized [5, 6]. This led to the recognition that a single hormone was responsible for both the vasopressor and antidiuretic effects observed previously. Much subsequent work focused on synthesizing peptide analogues that had similar activity as that of the natural

hormone. This interest later shifted to synthesizing analogues that were more potent and specific with regard to either vasopressor or antidiuretic effect. Finally, attention focused on formulating AVP antagonists, which displayed either vasodilatory or diuretic properties. In 1981, Manning et al. identified the first peptide VRAs in rats, and peptide antagonists with diuretic properties were first extensively studied in this species [7].

Two major disadvantages to peptide VRAs were evident early and restricted their clinical use. Most importantly, when administered chronically, peptides lost their antagonist effect and displayed agonist effects. Further making them clinically suboptimal were their short half-life, poor oral bioavailability, and species-specific activity [3, 6].

A significant breakthrough in the quest for a clinically useful compound came in 1992 when Yamamura et al. characterized OPC-31260 [8, 9]. This non-peptide selective V2 receptor antagonist was developed by performing a series of modifications to a previously identified non-peptide V1 receptor antagonist. OPC-31260 inhibited AVP binding to both V1 and V2 receptors, but was 100 times more selective for the V2 receptor, explaining its aquaretic effect. Compared to its peptide predecessors, OPC-31260 had more clinical promise because of its longer half-life and oral bioavailability and because its chronic administration did not result in any antidiuretic agonist activity [8]. Subsequently, several other non-peptide V2 receptor antagonists were developed and tested in preclinical studies. These studies confirmed that the compounds blocked AVP-induced cAMP production limiting AQP2 insertion into the apical membrane. Also observed was decreased AQP2 mRNA expression in the kidney. Molecular modeling studies have shown that V2 receptor binding sites for AVP and these agents partially overlap [10]. While AVP binds the V2 receptor more superficially, the antagonists compete with AVP by binding more deeply into a transmembrane pocket of the receptor (see Fig. 11.1). A dose-dependent aquaretic effect was demonstrated in both dehydrated and normally hydrated animals, as well as in animal models of water retaining states such as the syndrome of inappropriate antidiuretic hormone secretion (SIADH), cirrhosis, and chronic heart failure (CHF). There were no apparent adverse effects such as hypotension or tachyphylaxis [9]. Ohnishi et al. were the first to study V2 receptor antagonists in humans; in 1993, they reported that OPC-31260 had a potent aquaretic effect in normally hydrated healthy men (see Fig. 11.2) [11].

Efficacy and Safety of VRAs for the Treatment of Hyponatremia

Five non-peptide V2 receptor antagonists, or vaptans, have been developed and approved for clinical use or tested in large clinical trials (see Fig. 11.3). The next section will introduce these vaptans and summarize the evidence for their efficacy and safety in the treatment of chronic hyponatremic disorders. Subsequent sections will offer further recommendations for the clinical use of vaptans and discuss their role in specific patient populations.

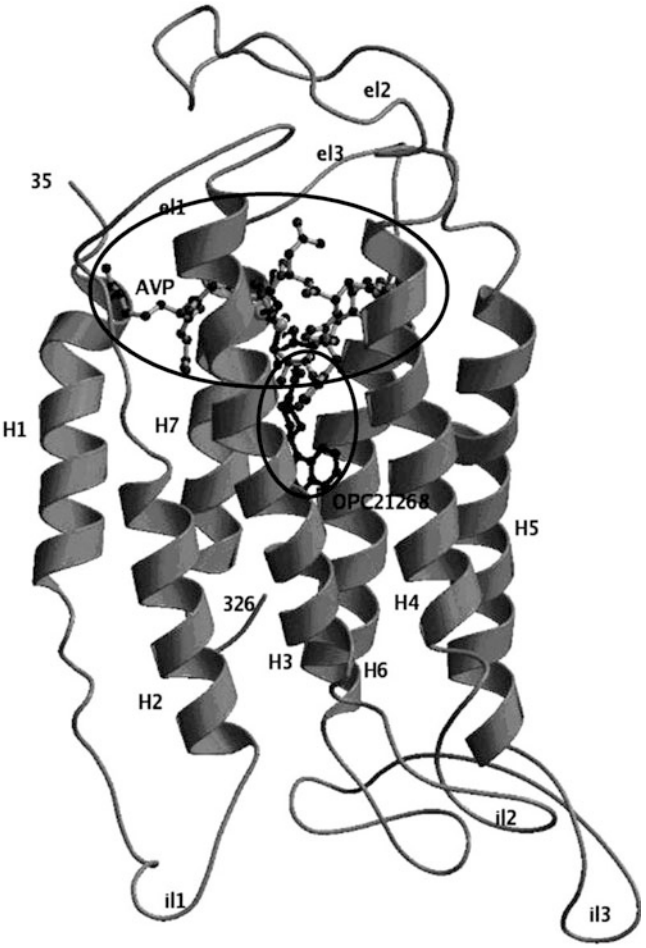

Fig. 11.1 V2 receptor shown as a *ribbon* diagram with superposition of *ball-and-stick* representations of AVP and the VRA, OPC-21268. The receptor loops labeled "e" are extracellular, whereas loops labeled "i" are intracellular. Transmembrane helices are labeled "H." AVP and the much smaller antagonists have distinct binding sites that partially overlap. The antagonist (*small oval*) binds deeply in the pocket and prevents AVP (*large oval*) from docking and interacting with the H7 transmembrane domain responsible for G protein activation. The figure was adapted with permission from Macion-Dazard et al. [10]

Mozavaptan

After the clinical utility of the compound OPC-31260 was discovered, it was commercially developed under the name mozavaptan (Physuline™, Otsuka). A study of 16 patients with paraneoplastic ectopic SIADH who received 30 mg

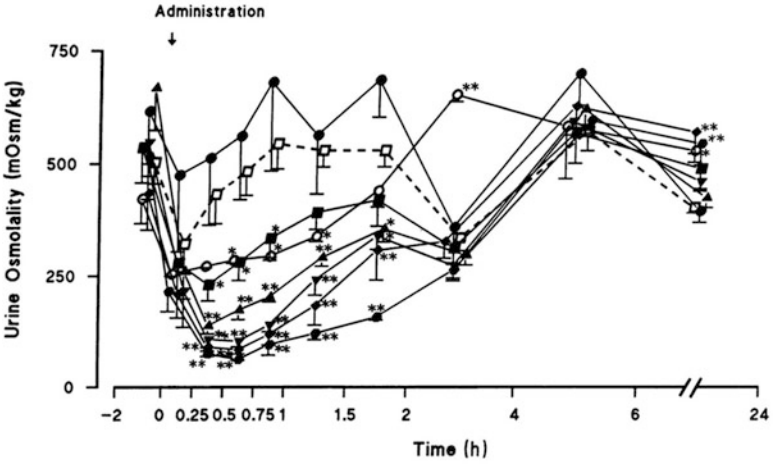

Fig. 11.2 Effects of the non-peptide V2 receptor antagonist, OPC-31260, compared to placebo and furosemide on urine osmolality in healthy, normally hydrated men. Volunteers were given single intravenous dosages of OPC-31260 ranging from 0.017 to 1.0 mg/kg (all *closed shapes*), placebo (*open squares*), or furosemide 0.33 mg/kg (*open circles*). Due to greater free water clearance, higher dosages of OPC-31260 significantly decreased urine osmolality more than furosemide for up to 4 h ($p < 0.05$). Compared to placebo, higher dosages of the vaptan produced a significant drop in urine osmolality within 15 min; this effect persisted through 2 h after administration. $*p < 0.05$; $**p < 0.001$ compared to placebo. Reproduced with permission from Ohnishi et al. © The American Society for Clinical Investigation, Inc. [11]

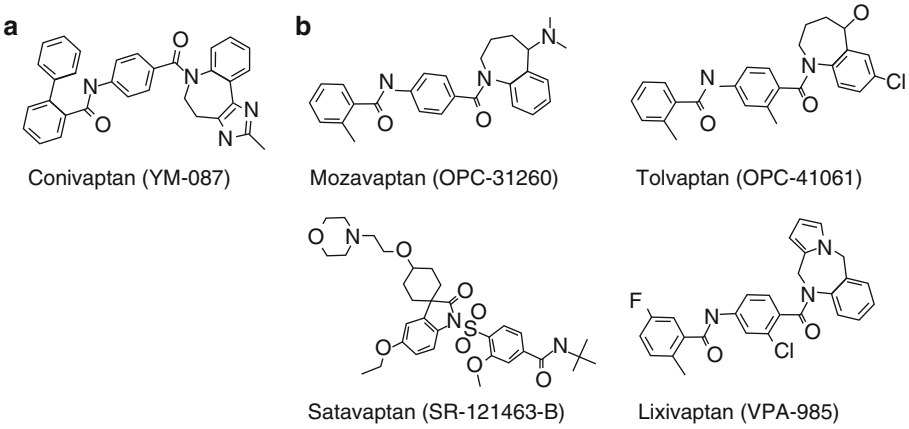

Fig. 11.3 Chemical structures of VRAs studied in large clinical trials. (**a**) Nonselective V1a/V2 receptor antagonist; (**b**) selective V2 receptor antagonists

daily for 7 days evaluated the short-term efficacy and safety of this drug [12]. Mean serum sodium concentration at baseline was 122.8 ± 6.7 mmol/L and increased to 133.3 ± 8.3 mmol/L at the end of the study. At 24 h after the first dose, mean serum sodium was 129.1 ± 5.7 mmol/L. Cumulative 24-h urine volume

increased after the first day of treatment, while urine osmolality decreased in the first 2 days. The most common adverse event was dry mouth, which occurred in five patients; less commonly observed side effects were malaise, decreased appetite, and nocturia as well as hypocalcemia and increased levels of potassium, aspartate aminotransferase, serum lactate dehydrogenase, or blood urea. Based on this study, in 2006, mozavaptan was approved in Japan for use with paraneoplastic SIADH.

Satavaptan

Satavaptan (Aquilda™, Sanofi-Aventis) was developed from the compound, SR-121463-B. It was under regulatory review in Europe until the sponsor withdrew its marketing application in 2008. The drug was developed after it was found to be a potent V2 receptor antagonist with highly selective V2 receptor affinity. Moreover, compared to OPC-31260, it had a similar aquaretic profile but markedly higher oral efficacy [13]. Satavaptan was studied in a placebo-controlled phase II trial of 34 patients with mean serum sodium level of 127 ± 2 mmol/L due to SIADH [14]. In the initial, double blind period of the study, patients were randomized to either satavaptan or placebo for up to 5 days. They were maintained in this group during a 23-day open-label dosage-adjustment period. Patients were asked to maintain a fluid restriction of 1,500 mL per day. Those that normalized or increased serum sodium by at least 5 mmol/L were classified as "responders." There was a dose-dependent effect on correction of serum sodium: 79 % in the 25 mg group (mean serum sodium 136 ± 3 mmol/L), 83 % in the 50 mg group (mean serum sodium 140 ± 6 mmol/L), and 13 % in the placebo group (mean serum sodium 130 ± 5 mmol/L) were responders. Lack of response to satavaptan was attributed mostly to increase in thirst and water intake in some patients, while others had a decrease in plasma drug concentration that could be explained by the concomitant use of carbamazepine, a known CYP3A inducer. Three patients had a correction of serum sodium greater than 12 mmol/L in the 24 h after the first dose of satavaptan. A slight increase in thirst was noted in both dosage groups. There was a moderate reduction in standing systolic (−6 ± 23 mmHg) and diastolic (−8 ± 14 mmHg) blood pressure in the high dose group. No serious drug-related adverse events were recorded.

During the second part of this study, long-term efficacy and safety were assessed for 12 months. Of the 18 patients who were included in the long-term study, ten remained on satavaptan for at least 12 months with maintained effectiveness and good tolerance. No adverse events related to the drug were reported during this period.

Lixivaptan

A different selective V2 receptor antagonist, lixivaptan (Cornerstone), was developed from the compound VPA-985 and is currently being investigated in phase III clinical trials. In one phase II study, 44 patients with hyponatremia related to cirrhosis, CHF, or SIADH were randomized to placebo versus lixivaptan 25, 125, or 250 mg twice daily for 7 days while maintained on fluid restriction [15]. In patients receiving lixivaptan, there was a dose-dependent decrease in urine osmolality and increase in free water clearance, urine output, and serum sodium concentration (see Fig. 11.4). Twelve patients exited the study early (half due to postural hypotension). Patients in the largest dose group more frequently had increased thirst, postural hypotension, and over-rapid correction in serum sodium concentration during the first 24 h. Excessive correction requiring the study drug to be withheld occurred in five patients in the highest dosage group, while it was only observed in two patients in the other lixivaptan dosage groups collectively. Excessive correction did not result in any neurologic adverse events.

More recently, lixivaptan was studied in nonhospitalized patients with chronic euvolemic hyponatremia, as defined by serum sodium level <135 mmol [16]. Patients were randomly assigned to receive either placebo ($n = 52$) or oral lixivaptan ($n = 154$), which was started at 25 mg daily and titrated as needed to a maximum dose of 100 mg daily, based on daily serum sodium measurements. Patients were treated for a maximum of 24 weeks. Lixivaptan significantly increased serum sodium concentration from baseline to day 7 more effectively than placebo (3.2 ± 0.5 versus 0.8 ± 0.6 for lixivaptan and placebo groups, respectively). Higher serum sodium levels were maintained over the 24-week period in the lixivaptan group, with less conservative fluid restriction requirements compared to the placebo group. The investigators reported that adverse events related to the study drug were mild to moderate and did not lead to discontinuation. Furthermore, they observed that lixivaptan could safely be titrated in the outpatient setting without any major events of over-rapid sodium correction.

Conivaptan

Conivaptan (Vaprisol™, Astellas) is the only V1a/V2 receptor antagonist that has been investigated in humans. In 2001, Decaux reported successfully using an oral dose of conivaptan 20 mg twice daily to treat chronic, symptomatic hyponatremia due to SIADH in two patients who were requiring long-term urea and furosemide therapy [17]. Both patients had a 6–8 h aquaresis after drug administration without any significant adverse hemodynamic consequences, which enabled them to maintain serum sodium levels 135 mmol/L or greater throughout the 3-month study period.

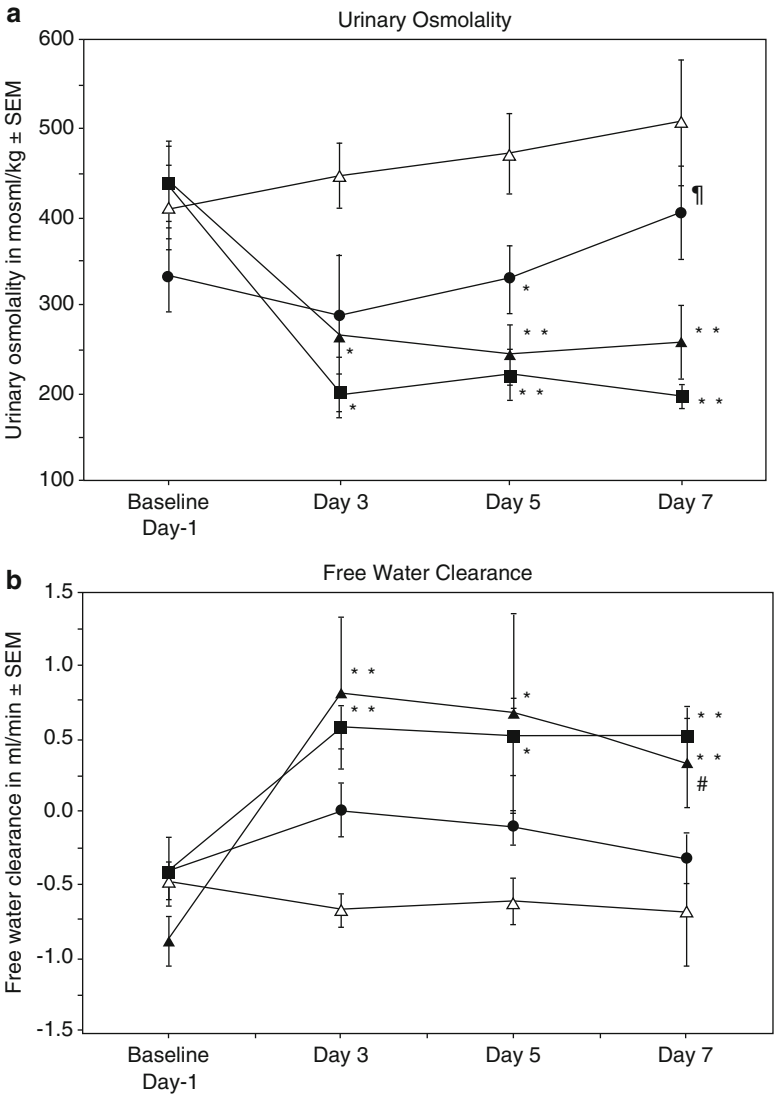

Fig. 11.4 Effects of lixivaptan on free water clearance and urine osmolality in patients with hyponatremia of various causes. Forty-four patients were randomized to receive twice daily doses of lixivaptan 25 mg (*closed circles*), 125 mg (*closed squares*), 250 mg (*closed triangles*), or placebo (*open triangles*) for 7 days. (**a**) Urine osmolality decreased in all dosage groups; in the two highest dosage groups, it remained significantly less than placebo throughout the study period. (**b**) Free water clearance increased in a dose-dependent manner. *$p < 0.05$, **$p < 0.01$, #$p < 0.05$ versus 25 mg twice daily, ¶$p < 0.05$ versus 125 mg twice daily. Reproduced from Wong et al., with permission from John Wiley & Sons, Inc. [15]

Several larger randomized, double-blind, placebo-controlled trials have also established the efficacy of conivaptan in patients with hyponatremia due to SIADH, CHF, and cirrhosis. In one study, 74 patients with euvolemic or hypervolemic hyponatremia (serum sodium concentration 115–130 mmol/L) were randomly assigned to placebo or oral conivaptan 40 or 80 mg/day in two divided doses for 5 days, along with fluid restriction [18]. Compared to placebo, the mean change from baseline in the serum sodium concentration area under the curve was significantly greater in the conivaptan groups (2.0-fold and 2.5-fold for conivaptan 40 and 80 mg/day, respectively). Patients given either conivaptan dose demonstrated a significantly shorter time to a 4 mmol/L or greater rise in serum sodium above baseline and were able to sustain this increase for a greater period of time than placebo-treated patients. The mean change from baseline in serum sodium concentration was 3.4 mmol/L, 6.4 mmol/L, and 8.2 mmol/L in the placebo, 40 mg/day, and 80 mg/day groups, respectively. Patients receiving conivaptan had significantly increased solute-free water clearance and plasma osmolality, along with decreased urine osmolality by study day 1. Incidence and types of adverse effects were no different in the conivaptan and placebo groups. Of the 51 patients that received conivaptan, three patients in the 40 mg/day group and two patients in the 80 mg/day group each had single episodes of over-rapid correction in serum sodium concentration based on the study criteria, which included an increase greater than 12 mmol/L per day. There were no adverse effects related to the greater than desired correction. Similar results have been reported in another trial of oral conivaptan, which randomly assigned 83 patients with euvolemic or hypervolemic hyponatremia to placebo or oral conivaptan 40 or 80 mg/day for 5 days [19].

Another trial involved 84 euvolemic or hypervolemic hyponatremic patients who were randomly assigned intravenous placebo or conivaptan administered as a 30 min, 20 mg loading dose followed by a 96-h infusion of either 40 or 80 mg/day [20]. Both conivaptan doses achieved a greater area under the serum sodium concentration time curve during the treatment period, compared to placebo. The mean increase in serum sodium concentration after 4 days was 0.8 ± 0.8 mmol/L, 6.3 ± 0.7 mmol/L, and 9.4 ± 0.8 mmol/L in the placebo, 40 mg, and 80 mg/day groups, respectively. The major adverse effect seen in the conivaptan groups were infusion-site reactions in a small number of patients, leading to withdrawal of one patient receiving 40 mg/day and four patients in the 80 mg/day group. The infusion-site reactions have been attributed to the propylene glycol vehicle used in the original drug formulation, which has now been replaced by a prediluted formulation without propylene glycol.

The United States Food and Drug Administration (FDA) has approved intravenous conivaptan for short-term use in hospitalized patients with euvolemic or hypervolemic hyponatremia. The drug is a potent inhibitor of CYP3A4, the enzyme responsible for the metabolism of many drugs. The oral formulation of conivaptan is no longer being developed for clinical use because of concern for serious drug–drug interactions if used for long periods of time. Coadministration of conivaptan with other potent CYP3A inhibitors such as ketoconazole, itraconazole,

clarithromycin, ritonavir, and indinavir is contraindicated. Recommended dosing of conivaptan is a 20 mg intravenous bolus dose over 30 min, then 20 mg infusion over 24 h. Based on its effect on serum sodium concentration, the continuous infusion dose may be increased to a maximum of 40 mg/day or omitted. The FDA label stipulates that the duration of treatment should not exceed 4 days.

Tolvaptan

Tolvaptan (OPC-41061, Samsca™, Otsuka) is a selective V2 receptor antagonist that was created via a series of structural conversions of OPC-31260. This new compound caused a dose-dependent increase in electrolyte-free water excretion in rats, and compared to OPC-31260, it was a more potent antagonist to human V2 receptors [21]. An initial phase 1 trial demonstrated that single oral doses of tolvaptan 60–480 mg increased mean serum sodium concentration, plasma osmolality, free water clearance, and urine volume in healthy subjects [22]. Frequent urination, dry mouth, and excessive thirst, but no dose-limiting toxicities, were observed.

Several large clinical trials have since demonstrated the therapeutic efficacy and safety of tolvaptan in hyponatremia. SALT-1 and -2 (Study of Ascending Levels of Tolvaptan in hyponatremia 1 and 2), two identical double blind, placebo-controlled, multicenter trials involving 448 patients with euvolemic or hypervolemic hyponatremia (serum sodium concentration $\leq$ 135 mmol/L), provide the strongest support [23]. The study protocol required that the disease entities of CHF, cirrhosis, and SIADH were equally divided among study patients, and also that at least 50 % of enrolled patients had a serum sodium concentration $<$ 130 mmol/L. Patients were randomized to receive oral tolvaptan 15 mg or placebo once daily for 30 days. According to the protocol, the dosage could be increased up to 60 mg/day over the initial 4 days of therapy based on the effect on serum sodium concentration. Though the drug was initiated in the hospital setting, the majority of the follow-up during the study period was conducted in the outpatient setting. Fluid restriction was not mandated. Tolvaptan increased the daily area under the curve for serum sodium concentration significantly more than placebo from baseline to day 4 and throughout the entire 30-day study period. Patients receiving tolvaptan had significantly greater net negative fluid balance leading to higher serum sodium concentration as soon as 8 h after drug administration. Furthermore, by study day 4, significantly more had normal serum sodium concentrations compared to placebo. In the tolvaptan group, the serum sodium concentration fell back to baseline after withdrawal of the drug at the end of the study period (See Fig. 11.5).

As a secondary end point, the SALT investigators examined the effect of tolvaptan on the change from baseline in the self-assessed SF-12 General Health Survey, a previously validated tool to measure physical and mental health status. There was no significant difference between groups receiving placebo or tolvaptan

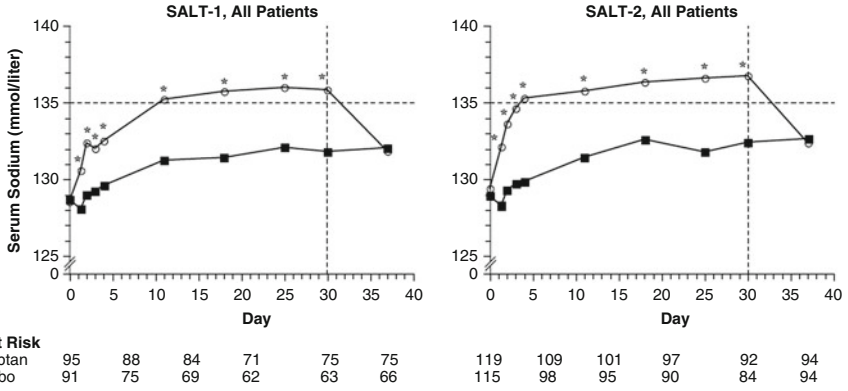

Fig. 11.5 Effects of tolvaptan on serum sodium concentration in patients with hyponatremia of various causes in the SALT-1 and -2 trials. Two identical double-blind, placebo controlled trials involving a total of 448 patients were conducted at 92 sites in the USA or abroad. A total of 225 patients (*open circles*) received tolvaptan, initiated at a dose of 15 mg/day and titrated to 30 mg/day or 60 mg/day as needed; 223 (*closed squares*) received placebo. Tolvaptan caused a robust, but safe increase in serum sodium levels during the first 4 days after initiation. Throughout the 30-day study period, serum sodium levels were significantly greater in patients treated with tolvaptan, compared to those receiving placebo (*$p < 0.001$). After discontinuation of the study medication on day 30 (*dotted vertical line*), serum sodium reverted to levels equivalent to those in the placebo group within 7 days. Reproduced with permission from Schrier et al.; © Massachusetts Medical Society [23]

in the physical component of the survey. The results did suggest that the vaptan improved self-assessed mental health. Compared to the placebo group, those treated with tolvaptan for 30 days had a clinically significant improvement in the mental health component of the scale, as shown by the combined analysis of all patients, those in SALT-1, and the subgroup of all patients with serum sodium level < 130 mmol/L. A trend to benefit was also observed in SALT-2 ($p = 0.14$), but because the drug did not satisfy the prespecified criterion of a statistically significant effect in two independent trials, the FDA-approved labeling states that the drug, like all vaptans, has not been shown to improve symptoms in hyponatremia.

The safety analysis in SALT-1 and -2 showed that thirst and dry mouth, the most common adverse effects, occurred more frequently in the treatment group than in the placebo group. Other common side effects including ascites, constipation, diarrhea, vomiting, fatigue, edema, weakness, urinary tract infection, hyperglycemia, hyperkalemia, dizziness, headache, and hypotension were reported in both groups equally. Alleviating a major concern regarding over-rapid correction of hyponatremia, only four patients receiving tolvaptan (1.8 %) had correction of serum sodium concentration >0.5 mmol/L/h during the first 24 h of the study. There were no events concerning for osmotic demyelination.

The long-term safety and efficacy of tolvaptan was demonstrated in another study, SALTWATER (Safety and sodium Assessment of Long-term Tolvaptan

With hyponatremia: A year-long, open-label Trial to gain Experience under Real-world conditions) [24]. This 4-year sequential, open-label extension enrolled 111 individuals who had completed the 30-day treatment phase and 7-day follow-up period in the SALT-1 and -2 trials. Whether they had received tolvaptan or placebo, patients were entered into SALTWATER at least 7 days (and up to 2–3 years) after the final study drug dose was received in SALT-1 or -2. They were initiated on a tolvaptan dose of 15 mg by mouth daily which was increased in 15 mg/day increments (up to a maximum of 60 mg daily) until a stable dose that maintained serum sodium concentration between 135 and 145 mmol/L was determined. Fluid restriction was not mandated but was permitted, along with use of other standard hyponatremia therapies such as demeclocycline and urea. Patients were followed for a mean of 701 days. Sixty-four patients discontinued treatment for a variety of reasons. The most common potentially treatment-related adverse effects were increased urinary frequency (9.9 %), thirst (9 %), and fatigue (5.4 %), as well as dry mouth, polydipsia, polyuria, hypotension, hypernatremia, dizziness, headache, peripheral edema, and acute renal failure (3.6 % each). There were no clinically significant changes in vital signs, electrocardiogram, or laboratory parameters (other than serum sodium and chloride concentration) during the follow-up period. Serum sodium correction exceeded 1 mmol/L/h in only five patients at the 8-h time point. Eighteen patients were found to have a serum sodium concentration >145 mmol/L at any time point; however, only one needed to be withdrawn from the study. The mean baseline serum sodium concentration was 130.8 ± 4.4 mmol/L. Mean serum sodium concentration corrected at a similar rate during the first 8 h as in the SALT-1 and -2 trials reached a similar plateau by 14 days and was sustained in the normal range throughout the greater than 4-year follow-up period.

Tolvaptan has been approved in the USA for treatment of euvolemic and hypervolemic hyponatremia, and in the European Union for therapy of hyponatremia due to SIADH. It should be started at a dose of 15 mg by mouth daily and may be increased by 15 mg each day up to a maximum of 60 mg/day, based on the effect on serum sodium concentration. Therapy should be initiated and reinitiated in an inpatient setting. To mitigate against too rapid correction, the labeling calls for avoidance of fluid restriction for the first 24 h. Tolvaptan is primarily metabolized by CYP3A and is a substrate and inhibitor of P-glycoprotein. Its simultaneous use with other CYP3A inhibitors should be avoided, and it is contraindicated with strong CYP3A inhibitors.

Clinical Use of Vaptans in Hyponatremia

The large amount of data collectively gathered from the numerous clinical trials described above validates the efficacy and safety of vaptans for the treatment of hyponatremia in states of inappropriate (SIADH) or maladaptive (CHF, cirrhosis)

AVP secretion. The appropriate use of vaptans has also been discussed and put into perspective elsewhere [25–27]. Several important limits to the use of vaptans apply. It should be emphasized that vaptans are not indicated to correct hyponatremia in hypovolemic patients. Rather, such patients should be treated with volume repletion, which will eliminate the volume stimulus to AVP release, leading to a water diuresis that can rapidly correct the hyponatremia (the rate of rise of serum sodium after resolution of hypovolemia may be so fast that the principal concern is avoidance of over-rapid correction).

Due to obvious ethical concerns, no placebo-controlled trial of a vaptan enrolled patients with severe symptoms such as seizures or a markedly impaired sensorium, and no trial has compared vaptans with standard therapy (hypertonic saline) for the treatment of such patients. Thus, there are no data on the use of vaptans in patients who require emergent correction of hyponatremia. Until further information about the use of vaptans in this clinical setting is available, severely affected hyponatremic patients should still be treated conventionally with hypertonic saline.

The efficacy of vaptans depends on the presence of relatively normal renal function. They have not been well evaluated in patients with significantly impaired renal function. Based on their mechanism of action, vaptans are unlikely to have any benefit in patients with a marked reduction in glomerular filtration rate, and they are contraindicated in anuric patients and in individuals receiving renal replacement therapy.

At present, another important consideration for clinicians is the cost–benefit of vaptan therapy. The current average wholesale price of tolvaptan is $300 per 15 or 30 mg tablet; making the minimum cost of a 10-day treatment $3,000 [28]. Conivaptan is even more expensive (especially considering that it requires inpatient administration); a 20 mg vial costs about $520, and the drug cost for a 4-day treatment can be as much as $4,160. The cost of long-term treatment with a vaptan is prohibitively high for most patients without health insurance, or for those patients whose insurance carrier will not provide coverage for its use. Making the task of considering cost–benefit even more complicated is that the benefit of improving serum sodium levels with vaptans has not been rigorously proven. Clinicians are aware that raising serum sodium in individual patients with chronic hyponatremia can correct CNS symptoms. As further suggested in SALT-1 and -2, improvement in cognitive function or mental health status may be a benefit that vaptans are able to provide by improving hyponatremia, but these findings were statistically significant only in SALT-1 (vide supra). The high cost of any therapy may be justified if it can save lives, but no vaptan trial to date has been powered to examine survival rates relative to treatment of hyponatremia. Another possible justification for the expense of vaptans may be if the cost burden of untreated or inadequately treated hyponatremia exceeds that of the therapy. Indeed, one analysis of the annual cost of hyponatremia in the USA estimated it to be $1.6–$3.6 billion [29]. Another study estimated that the presence of hyponatremia directly increased medical costs by

over 45 % over 1 year [30]. Though the verified efficacy of vaptans offers promise for reducing the overall cost of treating hyponatremia, data regarding hospital length of stay, hospital readmission, or comparisons of vaptans versus conventional therapies are still sparse.

At least until the pricing of vaptans decreases or more data regarding benefit beyond improving sodium levels emerges, clinicians will need to heavily weigh cost when deciding whether to initiate their use. It is important to estimate the anticipated length of treatment. For example, a patient with hyponatremia in the setting of a neurosurgical procedure may only have a transient need for vaptan therapy; alternatively, a patient with SIADH due to incurable malignancy would be expected to require prolonged use. If long-term use of a vaptan beyond hospital discharge is expected, one should ensure that the patient will be able to continually afford the medication prior to its initiation.

At the time of introduction of vaptans, there was a valid concern about the risk for osmotic demyelination due to over-rapid serum sodium concentration correction. Experience from clinical trials has lessened this concern, as (1) over-rapid correction occurred infrequently, and (2) in the rare cases when greater than desired correction occurred, it was usually easily controlled by a dosage decrease or by withholding a drug dose. There have been no reported cases of osmotic demyelination in any vaptan-treated patient or in any hyponatremic patient with a starting serum sodium concentration above 125 mmol/L. Nevertheless, at least until more extensive clinical trial evidence regarding outpatient initiation is available, the current recommendation is to initiate a vaptan only in hospital where frequent determinations of serum sodium can be made. Another necessary safeguard against excessive serum sodium correction is to avoid water restriction during the initiation period of vaptan therapy. Patients receiving vaptans should be managed in the same fashion as patients with nephrogenic diabetes insipidus of other etiologies. If a patient receiving a vaptan is unable to request water because of impaired mental status or if the ability to ingest water is impaired by intercurrent gastrointestinal disease, nil per os status, or intensive care unit admission with intubation and mechanical ventilation, vigilant monitoring of serum sodium concentration is mandatory. Clinicians should anticipate the need to reduce the dose or discontinue a vaptan if these circumstances develop.

Clinical Use of Vaptans in Chronic Heart Failure

The development and progression of CHF is characterized by a variety of maladaptive alterations in the neurohormonal axis [31]. Pharmacologic interventions directed at the hormonal excess in the sympathetic nervous system and the renin–angiotensin–aldosterone system including beta-blockers, angiotensin

converting enzyme (ACE) inhibitors, angiotensin receptor antagonists, and aldosterone antagonists have all been shown to have significant clinical benefit in CHF [32]. Also present in CHF are elevated or inadequately suppressed levels of AVP [31, 33]. Furthermore, the severity of heart failure directly correlates with the AVP level [34]. V1 receptor activation contributes to vasoconstriction, increased afterload, left ventricular hypertrophy, and remodeling. Additionally, V2 receptor activation leads to water retention and potentially, hyponatremia [32]. Several studies using different animal models have demonstrated that antagonism of either or both of these receptors is beneficial in CHF [35–38]. In one study that used rapid right ventricular pacing to induce congestive heart failure in dogs, selective V1a receptor antagonism with OPC-21268 resulted in significantly increased cardiac output and renal function, while selective V2 receptor antagonism with OPC-31260 resulted in significant aquaresis and increased serum sodium concentration [37]. OPC-31260 alone did not result in hemodynamic improvement, but had a synergistic effect when given in combination with OPC-21268; the combined V1a/V2 receptor antagonism improved cardiac output more than either agent alone.

The effect of dual V1a/V2 receptor blockade in CHF was studied in a trial in which 142 patients with NYHA class III or IV CHF were randomized to either placebo or a single intravenous dose of conivaptan 10, 20, or 40 mg [39]. Baseline characteristics including the use of beta-blockers and ACE inhibitors were similar in all groups. Predictably, relative to those receiving placebo, patients who received the single dose of conivaptan had a significant reduction in urine osmolality and dose-dependent increase in urine output during the first 4 h after the dose. Compared to placebo, conivaptan at doses of 20 and 40 mg significantly reduced pulmonary capillary wedge pressure (-2.6 ± 0.7, -5.4 ± 0.7, and -4.6 ± 0.7 mmHg for placebo, 20 mg, and 40 mg groups, respectively) and right atrial pressure (-2.0 ± 0.4, -3.7 ± 0.4, and -3.5 ± 0.4 mmHg for placebo, 20 mg, and 40 mg groups, respectively) during the 3–6 h interval after study drug administration. There was no significant difference in cardiac index, systemic and pulmonary vascular resistance, blood pressure, or heart rate between the conivaptan or placebo groups. This study examined the short-term, acute effects of conivaptan in CHF patients; no data examining the effects of long-term administration of a V1a/V2 receptor antagonist have been reported.

Selective V2 receptor antagonists, on the other hand, have been studied more extensively in CHF. The SALT-1 and -2 trials [23] included patients with CHF, and established the efficacy and safety of tolvaptan for the treatment of hyponatremia in this cohort. This was supported by other smaller trials which only included hyponatremic patients with CHF [40, 41]. After a few phase II trials suggested potential, focus shifted towards exploring other possible benefits of VRAs in heart failure. The large Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study with Tolvaptan (EVEREST) [42, 43] provides the most insights about the effects of selective V2 receptor antagonists on clinical status, morbidity, and

mortality in patients with CHF. EVEREST was composed of two identical short-term clinical status trials and a long-term outcome trial.

The short-term trials included a total of 4,133 patients who were hospitalized with acute decompensated heart failure. Those enrolled had to have documented evidence of impaired left ventricular function, but hyponatremia was not a requirement and only 7.7 % of enrollees had a serum sodium concentration less than 134 mmol/L. Patients were randomized to receive either tolvaptan 30 mg/day or placebo within 48 h of admission. Tolvaptan was given in addition to any standard heart failure therapies chosen by the treating physicians, including loop diuretics. The primary end point was a composite which incorporated changes in patient-assessed global clinical status and body weight at day 7 or discharge, whichever was first. Secondary end points included dyspnea, global clinical status, body weight, and peripheral edema. There was a modest benefit with tolvaptan according to the composite primary end point, which was driven exclusively by a 0.7 kg difference in change in body weight, as there was no difference in the patient-assessed global clinical status. Tolvaptan also provided a small benefit in the study's secondary measures of dyspnea and edema.

The long-term EVEREST trial comprised the 4,133 patients from the short-term trials who were continued on tolvaptan 30 mg/day or placebo for a minimum of 60 days in addition to standard CHF therapy. The dual primary end points were all-cause mortality and cardiovascular death or hospitalization for heart failure. The median duration of follow-up was 9.9 months. There was no difference between the two treatment groups in either of the primary end points. Tolvaptan did not provide any long-term benefit in the secondary end point of body weight. In the small number of patients with hyponatremia, tolvaptan provided a sustained benefit in correction of serum sodium concentration. As seen in other trials, long-term administration of tolvaptan was also safe in this cohort.

In summary, despite the attractive target of AVP excess in CHF, the collective clinical trial experience is that VRAs provide no benefit in improving heart failure symptoms, disease progression, or mortality. The only long-term vaptan trial was performed with the V2 selective agent tolvaptan. Whether long-term inhibition of the vasoconstrictor effect of V1a receptor activation with a combined V1a/V2 receptor antagonist or a selective V1a receptor antagonist would be beneficial are important unanswered questions. As VRAs have repeatedly been demonstrated to be effective and safe in treating hyponatremia in patients with CHF, hyponatremia remains the only role for their use at present.

Clinical Use of Vaptans in Cirrhosis

Patients with advanced cirrhosis frequently develop fluid retention, ascites, and hyponatremia. The most probable initial pathophysiologic process leading to this phenomenon is the development of sinusoidal hypertension, caused by distortion of the hepatic architecture and increase in hepatic vascular tone [44, 45]. This increase

in sinusoidal pressure leads to portal hypertension which, in turn, activates compensatory vasodilatory mechanisms. Nitric oxide overproduction, the predominant vasodilatory mechanism, causes splanchnic and peripheral arteriolar vasodilation. These events result in decreased effective arterial blood volume, and consequently, the activation of the renin–angiotensin–aldosterone system and sympathetic nervous systems and non-osmotic stimulation of release of AVP [46]. The elevation of AVP results in the development of impaired water excretion and hyponatremia in patients with advanced cirrhosis. The severity of liver disease directly correlates with the level of AVP. Furthermore, patients with impaired water excretion fail to adequately suppress AVP levels, even after a large water load [47].

Vaptans were demonstrated to increase electrolyte-free water excretion in cirrhotic rats [48, 49]. Though less well studied than in other populations, several small clinical trials have explored the effects of selective V2 receptor antagonists specifically in cirrhotic patients. The focus of these trials has been twofold (1) to ascertain whether selective V2 receptor antagonists are effective in treating hyponatremia in these patients and (2) to determine whether these agents provide benefit in fluid retention and management of ascites.

One trial examined the effectiveness of sodium correction in 60 cirrhotic patients with hyponatremia who were randomly assigned to placebo versus lixivaptan, 100 or 200 mg daily in divided doses given until normalization of serum sodium or up to 7 days [50]. All patients were on concomitant 1,000 mL fluid restriction. Serum sodium normalized in 27 % and 50 % of patients in the lixivaptan 100 mg group and 200 mg groups, respectively; but not in any patients receiving placebo. Among responders, the mean time to complete response was 4.8 days in the 200 mg group and 5.7 days in the 100 mg group. Mean change in serum sodium concentration was 1.8 ± 0.5, 0.8 ± 0.4, and 0.1 ± 0.2 mmol/L per 24 h in the 200 mg, 100 mg, and placebo groups, respectively. There was a dose-dependent reduction in urine osmolality and increase in urine volume. Compared to the placebo group, patients treated with lixivaptan more commonly developed an increase in thirst. There were similar rates of other adverse events in both lixivaptan and placebo groups.

Other studies have also supported the notion that, while vaptans are more effective than placebo, patients with cirrhosis may be less responsive to vaptans in achieving normalization of serum sodium levels as compared to patients with hyponatremia due to other causes. In one trial involving satavaptan and 110 patients with cirrhosis, overall, treatment with satavaptan was associated with improvement in hyponatremia compared to placebo; however, the percentage of responders at day 14 (as defined by those who had an increase in serum sodium $\geq$5 mmol/L from baseline or serum sodium level $\geq$136 mmol/L) was 26 %, 50 %, 54 %, and 82 % in placebo and satavaptan 5, 12.5, and 25 mg/day groups, respectively [51]. Furthermore, a subgroup analysis of the 120 patients with cirrhosis included in the SALT-1 and -2 trials showed that the proportion of cirrhotic patients achieving serum sodium $\geq$135 mmol/L at 30 days was 33 % in the tolvaptan-treated group and

19 % in the group receiving placebo ($p = 0.0838$) [52]. In the analysis of all patients together, relatively more tolvaptan-treated patients achieved normal serum sodium levels (56 % and 25 %, for tolvaptan and placebo, respectively) [23]. In the SALTWATER trial, patients with cirrhosis tended to have lower final serum sodium levels, although the study was underpowered to make this distinction conclusively.

The reasons for a less robust response to vaptans in patients with cirrhosis are not entirely known. One possibility is that higher doses may be required in this population to achieve the same effect as in other patients. Also, in patients with advanced cirrhosis, decreased delivery of the glomerular filtrate to the distal diluting segment due to avid proximal reabsorption of solute and water may be a factor. Another possibility is that V2 receptor independent pathways and receptors may play a role in AQP-2 regulation in cirrhosis [53].

Management of edema and ascites is a challenging issue in many patients with advanced cirrhosis. Several small clinical trials have studied the utility of selective V2 receptor antagonists given in addition to conventional diuretic therapy for the management of ascites, and have shown a modest short-term benefit in ascites improvement [51, 54, 55]. In a larger trial, the utility of satavaptan for the management of ascites was investigated in a total of 1,200 patients with cirrhosis who were included in three separate studies [56]. In study 1,463 patients with uncomplicated ascites not requiring paracentesis were randomized to placebo or satavaptan, in addition to conventional diuretics. The remaining patients had ascites requiring large volume paracentesis who were given either placebo or satavaptan, in addition to conventional diuretics (study 2, $n = 497$), or without concomitant diuretic therapy (study 3, $n = 240$). Patients were treated for 52 weeks in all three studies. There was no statistical difference between satavaptan and placebo with respect to the primary end points of worsening of ascites (study 1) and cumulative number of large volume paracentesis (studies 2 and 3) during 12 weeks.

Study 2 was stopped before treatment of all enrolled patients was completed due to higher mortality observed in the satavaptan group. At the end of 52 weeks, of the 328 patients assigned to satavaptan and 168 assigned to placebo, there were 101 deaths (30.6 %) in the satavaptan group, while 37 patients (22.3 %) receiving placebo died (relative risk 1.47, 95 % confidence interval 1.01–2.15, $p = 0.049$). The reasons for this observation are not entirely clear. Patients in the satavaptan and placebo groups had similar baseline characteristics. Though overall most causes of death in both groups were related to known complications of cirrhosis, the satavaptan group had a slightly higher percentage of deaths from non-hepatic causes, compared to patients receiving placebo (9.5 % and 3 %, respectively). The authors reported that non-hepatic causes of death in satavaptan-treated patients in study 2 were hypovolemia, thrombophilic disorders, cardiac events, respiratory disorders, cancers, and accidents such as falls. Study 3 was terminated early by the investigators due to futility. There was no difference in mortality in either arm of study 1 or study 3. According to the secondary end points of all three studies,

satavaptan only offered a slight benefit over placebo in delaying ascites formation. The only significant clinical benefit seen in all three studies was that satavaptan-treated patients had significantly less time to correction of hyponatremia compared to those receiving placebo.

In summary, though probably less robust in cirrhosis than other causes of hyponatremia, selective V2 receptor antagonists have clinical utility for the correction of hyponatremia in this challenging population. Despite initial phase II trials suggesting possible value in the management of ascites, a larger, longer-term trial has proven otherwise. The study reviewed above suggests a risk associated with satavaptan use in cirrhotic patients, at least when used for the purpose of fluid management. Whether this is drug specific or a class effect is unknown absent large-scale trials with other selective V2 receptor antagonists. V1a receptor antagonism in cirrhosis carries a risk of potentiating splanchnic vasodilation, and thus contributing to development of hypotension, hepatorenal syndrome, or variceal bleeding. For this reason, careful consideration must be given before the use of conivaptan, a nonselective V1a/V2 receptor antagonist, in patients with cirrhosis.

Concluding Comments

A large amount of data has been accumulated exploring the therapeutic possibilities of vaptans. Table 11.2 provides an overview of all large clinical trials in which they have been studied [14, 15, 18–20, 23, 24, 39, 40, 42, 43, 50, 51, 56–58]. The experience to date has not shown that vaptans provide a survival benefit. Nor do they alter the underlying disease processes in which AVP excess originates. Long-term trials have proven vaptans ineffective for management of extracellular fluid volume excess alone when given to patients with CHF or cirrhosis not selected according to serum sodium level; one study of satavaptan in patients with cirrhosis suggests that this drug, at least, may be harmful when used for this purpose. Other potential benefits such as improving cognition, decreasing hospital length of stay, or preventing hospital readmissions need to be better evaluated. The current high cost of vaptans is an impediment to their use in many situations.

Despite the current limitations, vaptans have been convincingly proven effective and well tolerated in the treatment of euvolemic and hypervolemic hyponatremia. With the clinical availability of vaptans, we now have a sophisticated tool, which, compared to conventional therapeutic options for hyponatremia, more directly and elegantly addresses the primary pathophysiology. The appropriate use of vaptans is summarized in Table 11.3. With increasing utilization, clinicians and patients will gain familiarity with use of the vaptans, and this new drug class will likely become a mainstay in the treatment of many hyponatremic disorders.

Table 11.2 Summary of published large clinical trials of vaptans

Author and study design	Study size and patient population	Intervention	Main end point(s)	Main result(s)
Soupart [14] RCT	$N = 34$ with hyponatremia due to SIADH	Satavaptan 25 mg/day vs. 50 mg/day vs. placebo, daily for 5 days; 18 patients subsequently enrolled in long-term trial for at least 12 months	Efficacy of improvement in hyponatremia over a 5-day period Long-term efficacy and safety	Responders (normalization of SNa level or increase $\geq$5 mmol/L) were 79 %, 83 %, and 13 % in 25 mg, 50 mg, and placebo groups, respectively. 18 patients included in the long-term study; ten were treated for at least 12 months with maintained effectiveness and good tolerance.
Gines [51] RCT	$N = 110$ with cirrhosis, ascites, and hyponatremia	Satavaptan 5 mg/day vs. 12.5 mg/day vs. 25 mg/day vs. placebo, daily for 14 days PLUS conventional diuretics	Change in body weight from baseline to day 14 Change in SNa level from baseline to day 5	Change in body weight of +0.49, +0.15, −1.59, and −1.68 kg for placebo, 5 mg, 12.5 mg, and 25 mg groups, respectively. Mean change in SNa level of 1.3, 4.5, 4.5, and 6.6 mmol/L for placebo, 5 mg, 12.5 mg, and 25 mg groups, respectively.
Wong [56] RCT	1,200 total patients[a] with uncomplicated ascites (study 1: $n = 463$), and difficult to treat ascites (study 2: $n = 497$ and study 3: $n = 240$)	Satavaptan (up to 10 mg/day) vs. placebo PLUS conventional diuretics (study 1) OR PLUS conventional diuretics after paracentesis (study 2) OR WITHOUT conventional diuretics after paracentesis (study 3) All groups treated for 52 weeks	Worsening of ascites as defined by paracentesis or weight increase $\geq$ 2 kg (study 1) or greater number of cumulative paracenteses over first 12 weeks (studies 2 and 3)	Satavaptan was not more effective than placebo in control of ascites in any of the three studies. Study 2 was stopped early due to increased mortality in the satavaptan group for unclear reasons (RR 1.47, 95 % CI 1.01–2.15, $p = 0.049$).

				Most deaths were related to known complications of cirrhosis. Study 3 was also stopped early due to futility.
Gerbes [50] RCT	$N = 60$ with cirrhosis and hyponatremia	Lixivaptan 100 mg vs. 200 mg both divided into twice daily doses vs. placebo for 7 days	Normalization of SNa level defined as $\geq$ 136 mmol/L	Normalization of SNa level in 27 % and 50 % of patients in the lixivaptan 100 mg group and 200 mg groups, respectively; but none in placebo group.
Wong [15] RCT	$N = 44$ with euvolemic and hypervolemic hyponatremia (33 patients with cirrhosis)	Lixivaptan 25 mg vs. 125 mg vs. 250 mg all twice daily vs. placebo for 7 days	Efficacy of improvement in hyponatremia and safety	Lixivaptan resulted in a dose-dependent increase in free water clearance, urine output, and SNa level, as well as a decrease in urine osmolality. The highest lixivaptan dose was more frequently associated with thirst, postural hypotension and excessive SNa level correction.
Abraham [40] RCT	$N = 42$ with symptomatic mild-to-moderate CHF[a]	Single dose of lixivaptan 10 mg vs. 30 mg vs. 75 mg vs. 150 mg vs. 250 mg vs. 400 mg vs. placebo WITHOUT conventional diuretics	Increase in urine volume over 4 h and 24 h.	During the first 4-h lixivaptan caused a dose-dependent increase in urine volume at all doses greater than 10 mg, and at 24 h in all dose groups (24-h urine volumes ranged from 1.8 L with placebo to 3.9 L after 400 mg).
Udelson [39] RCT	$N = 142$ with symptomatic moderate-to-severe CHF[a]	Single IV dose of conivaptan 10 mg vs. 20 mg vs. 40 mg vs. placebo WITHOUT standard CHF therapy	Peak change from baseline in PCWP at 3–6 h AUC for the PCWP change from baseline to 12 h	At 3–6 h PCWP was significantly reduced, compared to placebo, in the 20 mg and 40 mg groups

(continued)

Table 11.2 (continued)

Author and study design	Study size and patient population	Intervention	Main end point(s)	Main result(s)
				AUCs for PCWP vs. time through 12 h were significantly different in 20 mg and 40 mg groups (mean AUC in mmHg▪hours was −3.97, −29.8, and −26.8 for placebo, 20 mg and 40 mg groups, respectively)
Ghali [18] RCT	$N = 74$ with euvolemic or hypervolemic hyponatremia	Oral conivaptan 40 mg vs. 80 mg both divided into twice daily doses vs. placebo for 5 days	AUC for SNa level change from baseline to 5 days	Least-squares mean increase from baseline in the SNa level AUC was significantly greater in conivaptan groups, compared to placebo (6.4, 8.2, and 3.4 mmol/L for 40 mg, 80 mg, and placebo, respectively)
Zeltser [20] RCT	$N = 84$ with euvolemic or hypervolemic hyponatremia	Conivaptan 20 mg IV loading dose then 40 mg/day infusion vs. 20 mg IV loading dose then 80 mg/day infusion vs. placebo	AUC for SNa level change from baseline to 4 days	Least squares mean increase from baseline in the SNa level AUC was significantly greater in conivaptan groups, compared to placebo (6.3, 9.4, and 0.8 mmol/L for 40 mg, 80 mg, and placebo groups, respectively)
Annane [19] RCT	$N = 83$ with euvolemic or hypervolemic hyponatremia	Oral conivaptan 40 mg/day vs. 80 mg/day vs. placebo for 5 days	AUC for SNa level change from baseline to 5 days	Least squares mean increase from baseline in the SNa level AUC was significantly greater in conivaptan groups, compared to placebo (6.8, 9.8, and 1.2 mmol/L for 40 mg,

				80 mg, and placebo groups, respectively)
Gheorghiade [41] RCT	$N = 254$ with symptomatic mild-to-moderate CHF[a]	Tolvaptan 30 mg/day vs. 45 mg/day vs. 60 mg/day vs. placebo for 25 days PLUS stable doses of conventional diuretics	Change in body weight from baseline to day 14	Tolvaptan caused a significant decrease in weight compared to placebo after 24 h (−0.79, −0.96, −0.84, and +0.32 kg in 15 mg, 30 mg, 45 mg, and placebo groups, respectively) which was maintained during the study, but no further weight reduction was seen beyond day 1
Gheorghiade [57] RCT	$N = 319$ with symptomatic moderate-to-severe CHF[a]	Tolvaptan 30 mg/day vs. 60 mg/day vs. 90 mg/day vs. placebo for 60 days PLUS standard CHF therapy	Change in body weight from baseline to 24 h Worsening heart failure at 60 days defined as unscheduled visits for CHF, hospitalization, or death	Median body weight decrease was significantly greater in tolvaptan-treated patients at 24 h (−1.80, −2.10, −2.05, and −0.60 kg in 30 mg, 60 mg, 90 mg, and placebo groups, respectively) No difference in worsening heart failure between tolvaptan and placebo groups
Schrier [23] SALT-1 and −2 Two identical RCTs	$N = 448$ with euvolemic or hypervolemic hyponatremia	Tolvaptan 15 mg/day (titration up to 60 mg/day was allowed) vs. placebo for 30 days	Change in average daily AUC for SNa level from baseline to day 4 and change from baseline to day 30	Both trials showed similar results showing a significant increase in change in average AUC for SNa at days 4 and 30, compared to placebo
Berl et al. [24]. SALTWATER Open-label extension of SALT-1 and -2	$N = 111$ with euvolemic or hypervolemic hyponatremia	Tolvaptan (titration from 15 mg/day up to 60 mg/day per protocol) for up to 214 weeks	Long-term efficacy in treatment of hyponatremia and safety	Despite the large frequency of reported AEs in this chronically ill population (without a comparator group), only six occasions of AEs led to drug discontinuation

(continued)

Table 11.2 (continued)

Author and study design	Study size and patient population	Intervention	Main end point(s)	Main result(s)
				No new AEs from what were seen in short-term trials 60 % had normal SNa levels by week 50. Mean SNa level among all patients normalized during first 2 weeks and was maintained throughout the study
Gheorghiade [58] RCT	$N = 28$ with euvolemic and hypervolemic hyponatremia	Tolvaptan titrated up to 60 mg/day as needed without fluid restriction vs. fluid restriction plus placebo for up to 27 days	Change in SNa level from baseline to the last inpatient assessment	Tolvaptan increased SNa by the last inpatient assessment significantly greater than fluid restriction (5.7 and 1.0 mmol/L, respectively)
Gheorghiade [42] EVEREST short term Two identical RCTs	$N = 4{,}133$ with symptomatic moderate-to-severe CHF[a]	Tolvaptan 30 mg/day vs. placebo PLUS standard CHF therapy for up to 7 days or until hospital discharge	Changes in composite of self-assessed global clinical status and body weight	Compared to placebo, the tolvaptan group had a modest improvement in the composite end point; this was primarily a result of a 0.7 kg difference in body weight between the groups, as there was no difference in clinical status
Konstam [43] EVEREST long term RCT	$N = 4{,}133$ with symptomatic moderate-to-severe CHF[a]	Tolvaptan 30 mg/day vs. placebo PLUS standard CHF therapy for at least 60 days (median follow-up was 9.9 months)	All-cause mortality Cardiovascular death or hospitalization for heart failure	No difference in either end point related to long-term mortality or CHF-related morbidity Provides large safety database for tolvaptan

[a]Hyponatremia was not a required inclusion criteria

RCT randomized, placebo-controlled trial, *SNa* serum sodium, *IV* intravenous, *PCWP* pulmonary capillary wedge pressure, *AUC* area under the curve, *AE* adverse effects

Table 11.3 Key points about the appropriate use of vaptans

Establish the etiology of hyponatremia
• Vaptans are indicated only for euvolemic or hypervolemic hyponatremia
• Vaptans are not indicated for euvolemic disorders that reverse quickly, e.g., glucocorticoid deficiency
• Vaptans should not be relied upon to raise sodium concentration in patients with severe CNS symptoms that must be corrected urgently. Hypertonic saline is preferred in that instance
Omit fluid restriction during the first 24 h after initiation
Measure sNa level at baseline and every 6–8 h for the first 24 h
• Adjust fluid restriction based on rate of correction
Goal of correction is no different than for any other treatment for chronic hyponatremia
• Maximum correction limits of 12 mmol/L/24 h and 18 mmol/L/48 h apply
• Goal of approximately 6 mmol/L/24 h will improve CNS symptoms while limiting risk of exceeding correction limits
Measure U_{Osm} before and after the drug is begun to determine whether urine has become dilute. If response to drug inadequate:
• Titrate drug dose upward if U_{Osm} remains high
• Limit fluid intake if U_{Osm} is low
Patients with SIADH tend to be most responsive to vaptans and patients with cirrhosis least responsive
Recognize that if the drug works, the patient now has acquired nephrogenic diabetes insipidus
• Be aware of risk of rapid rise in sNa level if ability to ingest water or access to water becomes impaired by altered sensorium, intercurrent GI illness, n.p.o. status, intubation, etc.
• Reduce the dose or discontinue if access to water is restricted
• Adjust fluid administration accordingly
• Counsel patients on the risks

sNa serum sodium, U_{osm} urine osmolality, *GI* gastrointestinal, *npo* nil per os

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Chapter 12
Treatment of Hyponatremia

Richard H. Sterns, Stephen M. Silver, and John K. Hix

Introduction

Treatment of hyponatremia must meet three goals: (1) make sure the plasma sodium concentration does not decrease any further; (2) increase the plasma sodium concentration enough to prevent complications from the untreated electrolyte disturbance; and (3) avoid iatrogenic neurological injury caused by an excessive increase in the plasma sodium concentration [1, 2]. To meet these goals, clinicians must understand the physiological and pharmacological reasons for changes in plasma sodium levels and they must understand and respect the consequences of a rapid fall in the plasma sodium concentration, the adaptations of the brain to hyponatremia, and the hazard of raising the plasma sodium concentration once that adaptation has occurred. A full discussion of these principles is provided in the preceding chapters of this book and we will touch on them only briefly.

Preventing a Decrease in Plasma Sodium Concentration

The plasma sodium concentration is a function of three variables as described by Edelman's classic equation [3]

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$$\text{Plasma } [Na^+] \approx \frac{\text{Total body exchangeable } Na^+ + \text{Total body exchangeable } K^+}{\text{Total body water}}. \quad (12.1)$$

Thus, the plasma sodium concentration can fall if water is ingested and retained or if the concentration of sodium and potassium salts in the urine exceeds that of the plasma. Sodium and potassium losses in gastrointestinal fluid and sweat do not by themselves reduce the plasma sodium concentration because these losses are isotonic or hypotonic (with sodium plus potassium concentrations that are equal to or less than the concentration in plasma).

Fluid Intake

Restriction of oral fluid intake and avoidance of hypotonic tube feedings and intravenous fluids are essential components of management in all patients with untreated hyponatremia. Patients with acute hyponatremia caused by self-induced water intoxication, particularly runners and users of the street drug known as "ecstasy," may experience a spontaneous fall in plasma sodium concentration even if fluid intake is restricted [4]. In such patients absorption of ingested water can be delayed, with potentially disastrous consequences. For this reason, patients with these conditions must be managed aggressively, and urgent administration of hypertonic saline is wise to offset the effect of delayed water absorption. The plasma sodium concentration can be expected to fall by approximately 1 mEq/L for every 3 mL of water per kilogram of body weight [5]. Therefore, rapid absorption of a liter of ingested water will abruptly lower the plasma sodium concentration of a 50 kg subject by approximately 6 mEq/L. As will be discussed later in this chapter, administration of 150 mEq of sodium (300 mL of 3 % saline) will prevent such an acute decrease in sodium concentration from occurring; managing the risk of delayed water absorption is part of the rationale for treating acute symptomatic hyponatremia caused by self-induced water intoxication with 100 mL bolus infusions of 3 % saline at the start of therapy.

Excretion of Concentrated Urine

The plasma sodium concentration may fall spontaneously if the urine is hypertonic to plasma. This phenomenon, which has been called "desalination" can occur in two settings (a) patients with SIADH who have been volume expanded with intravenous fluids; (b) patients with renal salt wasting disorders [6, 7].

To understand the concept of desalination, consider a 50 kg woman with postoperative SIADH who has received 2 L of isotonic saline, each containing 154 mEq of sodium (See Fig. 12.1). In the presence of high levels of ADH, the urine

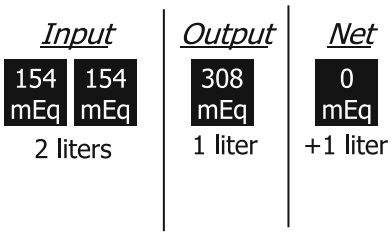

Fig. 12.1 Theoretical illustration of desalination. Two liters of 0.9 % saline, each containing 154 mEq of sodium are infused ("Input") and the entire 308 mEq of infused sodium is excreted in 1 L of urine ("Output"). The net effect is retention of 1 L of electrolyte-free water ("Net")

will become concentrated. As patients with SIADH are slightly volume expanded, infused sodium is excreted promptly in the urine. Therefore, all 308 mEq of infused sodium will be excreted in the urine, but at a higher concentration than isotonic saline. Assume that the urine sodium concentration is 308 mEq/L and that 1 L of urine is excreted. The net effect will be neutral balance for sodium (308 mEq infused and 308 mEq excreted) and 1 L of positive water balance (2 L infused and 1 L excreted). The infusion of 2 L of isotonic saline has resulted in a 6 mEq/L decrease in the plasma sodium concentration.

The theoretical concept of desalination illustrated above was validated in a series of young women undergoing elective surgery [6]. Operative procedures almost always result in temporary non-osmotic release of ADH and increased levels of the hormone often persist for 2 days or more [8]. High levels of ADH resulted in the excretion of concentrated urine, with cation concentrations (sodium plus potassium) as high as 390 mEq/L, far exceeding those in plasma. Even when patients received isotonic (0.9 % NaCl) or nearly isotonic (Lactated Ringers) fluids, the plasma sodium concentration fell [6].

Patients with subarachnoid hemorrhage are routinely given large volumes of intravenous fluids in an effort to maintain cerebral perfusion [9]. Like the response to surgery, acute intracranial insults can be expected to result in the non-osmotic release of ADH and the excretion of a concentrated urine (as discussed later, some investigators have attributed this finding to cerebral salt wasting). Thus, similar to the postoperative patient, patients with subarachnoid hemorrhage typically "desalinate" the infused isotonic fluid causing a decrease in the plasma sodium concentration [10, 11].

Increase the Plasma Sodium Concentration Enough

Acute Hyponatremia

Herniation is the most dreaded complication of hyponatremia [12, 13]. This is seen almost exclusively in patients with acute hyponatremia (usually less than 24 h) or in

patients with intracranial pathology. Most fatalities from hyponatremia have been reported in postoperative patients who were given hypotonic fluids intravenously and in marathon runners, psychotic patients, and users of ecstasy with self-induced water intoxication. Patients can rapidly progress from nonspecific symptoms, such as headache, nausea and vomiting, drowsiness or mild confusion, to seizures, respiratory arrest, and ultimately death or a permanent vegetative state as a complication of severe cerebral edema. Non-cardiogenic pulmonary edema and/or hypoventilation may occur, and the resulting hypoxia exacerbates brain swelling caused by the low plasma sodium concentration [14–18].

It is difficult to know how commonly fatal acute hyponatremia occurs. Except for a handful of single case reports, literature on the subject is dominated by a single author group which has reported large series of patients, mostly women of child bearing age and children who became hyponatremic after surgery [17, 19–22]. The source of these cases is uncertain, as the authors only indicate that these were "referrals" from multiple hospitals and that the authors played no role in management; one of these publications indicates that some of the referrals were from attorneys. A survey of 290,815 surgical procedures on females at the Mayo Clinic from 1976 to 1992 failed to identify any association of respiratory arrest with postoperative hyponatremia but did identify six cases of central pontine myelinolysis [23]. Nevertheless, regardless of how commonly it occurs, the fact that *some* patients rapidly progress from mild symptoms to death has led virtually all authors to the conclusion that symptomatic acute hyponatremia should be treated urgently with hypertonic saline.

Seizures can occur in both acute and chronic hyponatremia but are most common in patients whose plasma sodium concentration falls abruptly due to self-induced water intoxication (psychotic patients, runners, and users of ecstasy) [24, 25]. Seizures are surprisingly uncommon in patients with chronic hyponatremia, even when the plasma sodium concentration falls below 110 mEq/L [26, 27]; affected patients often have an underlying seizure disorder [28]. Seizures associated with hyponatremia are usually self-limited, but occasionally status epilepticus can develop; response to anti-epileptic medications can be poor unless the plasma sodium concentration is increased.

There is a paucity of data on how much increase in the plasma sodium is needed to reverse impending herniation or seizures, the most serious complications of hyponatremia. The first report of successful treatment of acute postoperative hyponatremia was published in 1938 [29]: a patient with seizures, coma, opisthotonos, Cheyne's stokes respirations, and bilateral Babinski's signs was rescued from what was most likely impending herniation with a 130 mL bolus of 5 % saline, the equivalent of 237 mL of 3 % saline; the dose administered would be expected to increase the plasma sodium of a 50 kg women by approximately 4 mEq/L. Textbooks of medicine in the 1950s recommended an infusion of 100–300 mL of hypertonic saline for the rare patient with severe symptoms from water intoxication [30]. More recently, a consensus conference on water intoxication in marathon runners appears to have rediscovered these old regimens, recommending that a 100 mL bolus of 3 % saline infused over 10 min be given in the field for severe symptoms, and that this

could be repeated twice if needed [31]. Experience with this regimen in a small number of runners has been favorable [32].

Few published papers include data on how much the plasma sodium increased after treatment of hyponatremic seizures and coma with hypertonic saline. A review of the available literature concluded that a 4–6 mEq/L increase is sufficient in these circumstances [2]. The largest single series reported on five patients with hyponatremic seizures who were given 29.2 % saline at the rate of 5 mL/min for 10 min (equivalent to 487 mL of 3 % saline); the author of this series mentioned that seizures stopped during the infusions, in one case during the first 5 min [33]. This suggests that a smaller volume might have been equally effective.

Recently, neurointensivists have turned to hypertonic saline rather than hypertonic mannitol to treat cerebral edema in normonatremic patients. Published experience with this intervention has been similar to what has been reported in patients with acute hyponatremia. A 4-year single center study of 63 patients treated for transtentorial herniation caused by a variety of neurosurgical conditions found that a 30 mL to 60 mL bolus of 23.4 % saline, which increased the plasma sodium by 5 mEq/L, promptly reversed clinical signs of herniation and reduced intracranial pressure by nearly 50 % within an hour; the dose of 23.4 % saline used is equivalent to 234 to 468 mL of 3 % saline [34]. In another study, infusion of a larger dose of 23.4 % saline (2 mL/kg), to patients with subarachnoid hemorrhage, increased the plasma sodium by 11.2 $\pm$ 4.0 mEq/L which increased cerebral perfusion pressure and decreased intracranial pressure by 93 %, in some cases to levels below 0 mmHg [35]. In a placebo-controlled study of patients with subarachnoid hemorrhage, infusion of 2 mL/kg of 7.2 % saline increased the plasma sodium by 4–7 mEq/L at 30 min and by 1–5 mEq/L after 210 min; an increase in plasma sodium of this magnitude was enough to decrease intracranial pressure and to increase cerebral perfusion pressure [36]. Based on these findings and a review of other published observations, the authors of this study would now recommend that the initial bolus be $<$2 mL/kg of the 7 % solution (equivalent to 235 mL of a 3 % saline solution in a 50 kg woman).

Severe Chronic Hyponatremia

Although patients with chronic hyponatremia rarely, if ever, succumb to cerebral edema, many clinicians are concerned that the risk of an adverse outcome is increased if the plasma sodium concentration is allowed to remain below a level thought to be "safe" (variably set at $>$120 or even $>$130 mEq/L). There is little evidence to support this belief, but unfortunately, it continues to influence clinical practice.

Soon after the Neurology literature linked central pontine myelinolysis with "rapid correction" of hyponatremia, reports appeared in the Internal Medicine and Nephrology literature asserting that failure to promptly raise the plasma sodium to a "safe" level increased the risk of mortality. For example, a review of the literature,

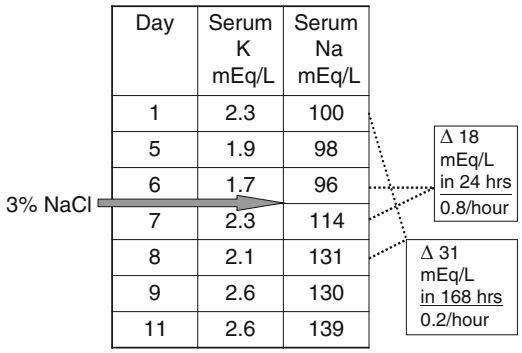

Fig. 12.2 A patient admitted with a plasma sodium of 100 mEq/L whose hyponatremia went untreated for 5 days was finally treated with hypertonic saline when plasma sodium had fallen to 96 mEq/L increasing the plasma sodium concentration by 18 mEq/L within 24 h (0.75 mEq/L/h) and by 35 mEq/L within 48 h (0.72 mEq/L/h); yet the correction could be misleadingly classified as "slow," because it took 168 h to correct the plasma sodium from the admission value of 100 mEq/L to a "safe" level above 130 mEq/L (0.18 mEq/L/h). Data from Tomlinson et al. [38]

cited in a widely quoted 1985 editorial, compared 30 severely hyponatremic nonalcoholic patients whose plasma sodium was raised to 130 mEq/L at a rate averaging 1.9 mEq/L/h to 26 patients whose plasma sodium was corrected by <0.6 mEq/L/h; mortality was said to be six times higher among patients who were corrected slowly [37]. The review cited mortality rates of 63 % in nonalcoholics and 86 % in alcoholic subjects with plasma sodium concentrations <105 mEq/L.

There were several flaws in this analysis. Most "rapidly" corrected patients had acute hyponatremia, and, as would be expected, they experienced no posttherapeutic complications. "Slowly" corrected patients had severe chronic hyponatremia (often with plasma sodium values <105 mEq/L) and many developed fatal central pontine myelinolysis (CPM) after treatment with hypertonic saline; their rate of correction was classified as "slow" (<0.6 mEq/L/h) even when correction over 48 h exceeded 25 mEq/L [38]. As shown in the example in Fig. 12.2, the calculation leading to this conclusion was quite misleading. Subsequent literature reviews and cohort series free of selection bias do not support the conclusion that slow correction of chronic hyponatremia increases mortality; on the contrary, as discussed below, attempts to raise the plasma sodium from an extremely low level to a "safe" level commonly leads to neurological morbidity.

A 5-year study of patients admitted to two teaching hospitals in Rochester, New York found that literature reviews exaggerate the true morbidity and mortality rates associated with plasma sodium concentrations ≤105 mEq/L; the study did not support the idea that rapid rates of correction were needed to ensure survival [26]. Only one of 19 patients died, an alcoholic who developed central pontine myelinolysis after treatment with hypertonic saline. Eight patients (including one with hospital-acquired hyponatremia) with plasma sodium concentrations ≤105 mEq/L enjoyed uneventful recoveries after correction to a plasma sodium

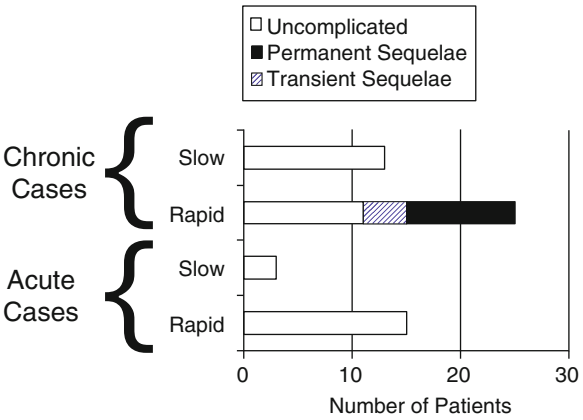

Fig. 12.3 Rate of correction and outcomes among patients with serum sodium concentrations ≤105 mEq/L identified by a survey of the membership of the American Society of Nephrology [39]. Acute patients were those with self-induced water intoxication due to psychosis and patients with hospital-acquired hyponatremia. Rapid correction is defined as >12 mEq/L in 24 h or >18 mEq/L in 48 h. Neurological sequelae only occurred in the chronic patients corrected rapidly (data from Sterns)

≥120 mEq/L at rates ranging from 0.21 to 0.55 mEq/L/h. These observations were subsequently confirmed in a much larger multicenter series of patients with plasma sodium concentrations ≤105 mEq/L [39] (Fig. 12.3).

The findings were also confirmed in a more recent 12-year study of all patients admitted to one of these Rochester hospitals. The study examined all deaths associated with a plasma sodium concentration <120 mEq/L [27]. As in other studies, mortality rates were higher in hyponatremic patients than in normonatremic patients and they progressively rose as the plasma sodium concentration fell from normal to 120 mEq/L. However, below 120 mEq/L, the trend reversed, so that, paradoxically, as the plasma sodium continued to fall, the mortality rate progressively decreased (Fig. 12.4). It appeared that deaths associated with hyponatremia were caused by severe underlying diseases rather than the electrolyte disturbance itself; i.e., patients died *with* hyponatremia rather than *from* hyponatremia. More than two-thirds of patients who died after experiencing a plasma sodium <120 mEq/L had at least two additional acute severe progressive illnesses, most commonly sepsis and multiorgan failure, and death was unlikely to be attributable to hyponatremia: many patients died long after hyponatremia had been corrected and for others, hyponatremia occurred as a terminal event after a protracted illness, after attempts at curative therapies had been withdrawn. Three deaths (5.6 %) in 12 years could plausibly be related to adverse consequences of hyponatremia, and only one (1.8 % of the fatal cases and 0.15 % of all patients with a plasma sodium <120 mEq/L) was from cerebral edema (a patient with a cerebrovascular accident following a carotid endarterectomy). It was concluded that the nature of underlying illness rather than the severity of hyponatremia best explains mortality associated

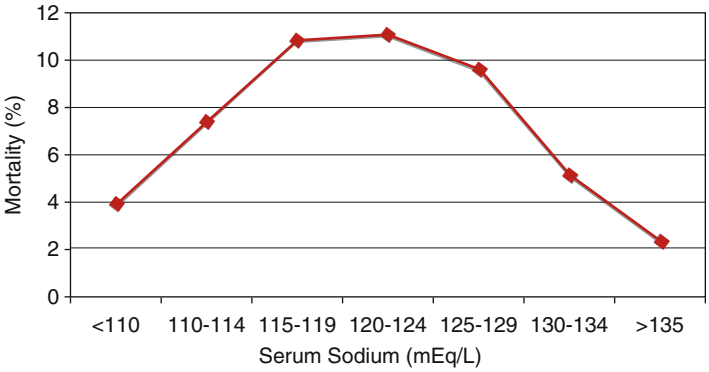

Fig. 12.4 Mortality rates and serum sodium values among 164,146 patients admitted to a single community teaching hospital between 1996 and 2007 [27] (with permission from CJASN)

with hyponatremia in hospitalized patients and that neurological complications from hyponatremia are uncommon among patients who die with hyponatremia. In most cases, a plasma sodium concentration <110 mEq/L was associated with medications and with mild gastrointestinal or respiratory conditions and, in contrast to patients with milder hyponatremia, severe underlying illnesses were infrequent. Survival after experiencing a plasma sodium <110 mEq/L could not be attributed to aggressive efforts to achieve a "safe" sodium level: correction averaged 9.3 ± 3.8 mEq/L in the first 24 h and 16.3 ± 4.9 mEq/L in the first 48 h of therapy; 69 % were corrected by ≤10 mEq/L/24 h, 75 % by ≤18 mEq/L/48 h, and 97 % by <25 mEq/L/48 h. In 75 % of survivors, the plasma sodium was still <120 mEq/L, 24 h after the lowest sodium value was recorded; no patient achieved a plasma sodium above 126 mEq/L in the first 24 h.

These findings are consistent with other series. For example, among 223 patients admitted to a single hospital in China for symptomatic hyponatremia caused by thiazide diuretics (plasma sodium 98–128 mEq/L), no patient died, only two developed seizures, there were no cases of non-cardiogenic pulmonary edema or coma, and only one patient developed permanent neurological sequelae (a patient with central pontine myelinolysis); 98 % of the patients were managed without hypertonic saline and the average correction in 24 h was 3 mEq/L (personal communication from the author) [40]. Similarly, a prospective series of 184 patients with symptomatic hyponatremia, representing all admitted patients with serum sodium concentrations <120 mEq/L (79 % of them chronic), reported favorable outcomes with very conservative management. Only 1 % of the patients were given hypertonic saline, 24 % were treated with fluid restriction alone, and 23 % received no therapy; there were no complications among 35 patients corrected by <4 mEq/L in 24 h [41].

A dramatically different perspective was offered by a case series published by the authors of the previously mentioned 1985 editorial. Similar to what they had reported for *young* women with acute postoperative hyponatremia [19], this group found an extraordinarily high incidence of respiratory arrests, hypoxia, death, and

severe neurological sequelae among 53 *postmenopausal* women with *chronic* hyponatremia (though it should be noted that the authors' definition of chronic hyponatremia allowed the inclusion of 16 postoperative cases) [21]. The unusual findings are best explained by the method of case finding. An almost uniformly dismal course was reported for 36 postmenopausal women with symptomatic, chronic hyponatremia who were referred to the authors for consultation but whose care they had not directed (as was true for the outcome studies of acute hyponatremia by the same group, it is unclear where the patients were treated or why the authors were consulted); all such cases had experienced respiratory arrests or severe hypoxia (PO_2 below 50 mmHg) requiring endotracheal intubation and mechanical ventilation. The outcome was particularly grim among 14 patients treated with fluid restriction alone; 11 of the 14 patients died, all but one within 24 h, and three patients had documented cerebral edema and evidence of herniation at autopsy. The 22 patients who received treatment with intravenous saline after hypoxia did not die within 24 h, but 14 were left permanently disabled, vegetative, or dead. We are not told if these patients had a clinical course consistent with osmotic demyelination syndrome (see below), but correction in the 22 cases averaged 30 mEq/L in 41 h, a rate that would be expected to cause iatrogenic injury. By contrast, and consistent with most other series, the authors reported a uniformly favorable outcome among 17 postmenopausal women that they had actually managed. All of these patients were given saline (but only 12 received hypertonic saline), resulting in correction by an average of 8 mEq/L within 12 h and 14 mEq/L within 24 h. These 17 cases included every postmenopausal woman with symptomatic chronic hyponatremia whose care was directed by the authors during a 9-year interval (an average of two patients per year).

Although death from chronic hyponatremia is uncommon, even when the plasma sodium is extremely low, the electrolyte disturbance causes distressing symptoms (e.g., weakness, confusion, delirium, gait disturbances, muscle cramps, nausea, and vomiting) that deserve treatment. Even what seems to be asymptomatic, mild chronic hyponatremia causes gait disturbances and disturbed cognition, and it markedly increases the risk of falls and fractures [42, 43]. Similarly, although the incidence may be low, hyponatremia increases the risk of seizures. Therefore, an attempt to increase the plasma sodium concentration is indicated in every patient with hyponatremia. However, as will be discussed next, correction should be limited to avoid iatrogenic injury.

Avoid Iatrogenic Injury

Osmotic Demyelination Syndrome

The term, "osmotic demyelination syndrome" (ODS) was introduced in 1986 at a time when there was a lot of skepticism that iatrogenic brain damage from excessive correction of hyponatremia was a serious concern [44, 45]. A 5-year study at

two institutions identified eight patients who had a neurological syndrome with clinical or pathological findings typical of central pontine myelinolysis. After presenting initially with severe hyponatremia, often associated with relatively mild neurological symptoms, each patient's condition worsened after correction by more than 12 mEq/L/day. Five of the patients were treated at one hospital, and accounted for all the neurological complications recorded among 60 patients with plasma sodium concentrations below 116 mEq/L; no patient in whom the sodium level was raised by less than 12 mEq/L/day had any neurological sequelae. These clinical findings can best be explained by the brain's adaptation to severe hyponatremia.

Patients whose plasma sodium concentrations fall gradually over days usually have undetectable brain edema and only mild to moderate neurological symptoms because of an adaptive loss of brain cell solutes (organic osmolytes) [12]. The adaptation to hyponatremia permits osmotic equilibrium between cells and extracellular fluid without requiring brain cells to accumulate extra water. During the onset of hyponatremia, brain cells become depleted of electrolytes and organic osmolytes; a maximal adaptation to a falling plasma sodium requires approximately 2 days, whereas it takes considerably longer to replace lost osmolytes when hyponatremia is corrected. Consequently, once adapted to hyponatremia, the brain is vulnerable to injury if the plasma sodium is normalized too rapidly. Too much correction of chronic hyponatremia in too short a time triggers a cascade of adverse events beginning with breakdown of the blood–brain barrier and culminating in the programmed death of oligodendrocytes, the cells that make myelin in the central nervous system [2, 46, 47]. The injury presents clinically as a delayed onset of progressive neurological findings that come after treatment (the "osmotic demyelination syndrome"). The condition is classically associated with lesions located in the central pons ("central pontine myelinolysis"), but lesions are equally common outside the pons ("extrapontine myelinolysis") [2, 46, 48–50]. Studies in experimental animals have shown conclusively that osmotic demyelination is caused by rapid correction of hyponatremia and not hyponatremia itself [2, 12, 46]. Consistent with this conclusion, re-lowering the plasma sodium concentration after excessive correction prevents demyelinating brain lesions and death in experimental models [51].

Several observations suggest that osmotic demyelination following rapid correction of chronic hyponatremia may be caused by slow uptake of organic osmolytes lost during the adaptation to a low plasma sodium concentration: brain regions slowest to recover organic osmolytes are injured the most [52]; rapid correction of hyponatremia in uremia, which rarely results in osmotic demyelination, is associated with more rapid reuptake of organic osmolytes, particularly myo-inositol [53]; and exogenous administration of myo-inositol decreases the severity of injury [54].

Rapid correction of chronic hyponatremia may be analogous to an acute hyperosmolar insult. Within 2–3 days, the adaptation to hyponatremia restores brain volume to near normal; normalizing the plasma sodium then dehydrates the brain just as acute hypernatremia dehydrates the brain in a normonatremic subject [55].

Indeed, hypernatremia can cause osmotic demyelination in patients without a history of hyponatremia [56].

If hyponatremia has only been present for a few hours, a rapid increase in plasma sodium concentration does not commonly result in osmotic demyelination in either animal models or in humans [2, 26, 57, 58]; profound acute hyponatremia due to absorption of glycine irrigant may be an exception (see below) [59]. In acute water intoxication, there is not enough time for a cerebral adaptation to hyponatremia. Patients with this condition often have an intact ability to excrete maximally dilute urine, and become transiently hyponatremic because of massive water intake exceeding a normal excretory capacity or because of brief self-limited ADH release caused by nausea, stress, or physical exertion. Once water intake stops, hyponatremia typically "auto-corrects" owing to the excretion of large volumes of dilute urine. Patients who have been hyponatremic for a few hours rather than days usually tolerate rapid correction of hyponatremia without developing neurological sequelae. Thus, efforts to limit correction of hyponatremia should be directed primarily at patients with chronic hyponatremia.

In addition to chronicity, several other risk factors for osmotic demyelination have been identified (1) a plasma sodium concentration $\leq$105 mEq/L; (2) hypokalemia; (3) alcoholism; (4) malnutrition; (5) liver disease [60]. These risk factors are based on analyses of the clinical characteristics of published cases of ODS, but they have not been studied in experimental models.

The most comprehensive description of ODS (central pontine and extrapontine myelinolysis) can be found in a classic single center study of 14 patients with neurological complications following correction of severe, symptomatic hyponatremia [61]. As in the 1986 description of ODS, patients' hyponatremic symptoms at presentation were variable, ranging from slight confusion to seizures. These initial encephalopathic symptoms improved after correction of hyponatremia only to be replaced about 3 days later by new, often permanent, neurological findings. Typically, spastic quadriparesis, pseudobulbar palsy, and impairment in the level of consciousness progressed for up to 7 days. Improvement generally began 2 weeks after correction and continued for up to a year in some patients. Brain imaging was normal in the initial week of illness, while later scans, showed central pontine and/or symmetric extrapontine lesions. Although this sequence of events typically followed an elevation in plasma sodium by more than 18 mEq/L/24 h, it sometimes followed a rise as slow as 10 mEq/L/24 h and 21 mEq/L/48 h.

A recent series of 12 patients with osmotic demyelination identified at a single tertiary medical center confirms findings from previously published single-center series [49]. Of the ten patients with plasma sodium levels that were known, one had severe acute hypernatremia (176 mEq/L due to a dialysis error) and six had severe hyponatremia ($<$110 mEq/L in four) that had been corrected rapidly. Patients with symptomatic hyponatremia initially improved after treatment, but then with a delay of 3–15 days a variety of neurological complications developed including rigidity, cardiorespiratory symptoms, autonomic dysfunction, seizures (generalized tonico-clonic and partial complex), altered consciousness, pyramidal, brainstem, and cerebellar signs, and neuropsychiatric problems (catatonia, emotional lability).

As has been reported previously, two patients had negative magnetic resonance images (MRI) 2–3 days after clinical manifestations of ODS, only to have subsequent positive studies 10 and 26 days later. Only two of the hyponatremic patients were known to be alcoholics. Two patients developed hyponatremia as a complication of the treatment of diabetes insipidus and corrected rapidly when desmopressin was stopped. Correction in the hyponatremic patients exceeded 18 mEq/L within 48 h in all cases, and it exceeded 25 mEq/L in 48 h in only three.

Osmotic demyelination is a relatively common complication of liver transplantation [62–64]. A recent series compared 11 patients with ODS after transplant to 44 controls matched for age, sex, and date of surgery. Patients with ODS were more likely to be hyponatremic prior to transplant (126 ± 7 vs. 134 ± 7 mEq/L; $p = .001$), and they had a significantly larger perioperative increase in plasma sodium than controls (16 ± 6 vs. 11 ± 5 mEq/L; $p = 0.002$) [65]. The reason for the association between liver disease and ODS is not known. Hyperammonemia is associated with brain cell swelling and depletion of brain myoinositol and other organic osmolytes [66]. Interestingly, typical ODS has been reported following rapid correction of acute hyponatremia caused by absorption of glycine irrigant during prostate surgery [59]; metabolism of absorbed glycine results in high levels of blood ammonia [67, 68].

Therapeutic Limits

In experimental animals, both the incidence and severity of demyelinating brain lesions increase with the magnitude and rapidity of correction. In the chronically hyponatremic rat, lesions can be induced by as little as 13 mEq/L if the increase in plasma sodium concentration is extremely abrupt, and most animals will develop lesions if correction exceeds 25 mEq/L within 24 h [69]. In the dog, the threshold for causing myelinolysis has been estimated to be 15 mEq/L within 24 h and 21 mEq/L within 48 h [70].

Six cohort studies [26, 39, 41, 59, 71, 72], including two prospective series [41, 59] and three literature reviews by three different authors [44, 73, 74], have concluded that rapid correction of chronic hyponatremia is more likely to be associated with neurological injury than slow correction. Estimates of how much correction of chronic hyponatremia is too much in humans have varied over the years.

A literature review in 1986 suggested a limit of 12 mEq/L in 24 h [44] and a 1987 study set the limit at 25 mEq/L in 48 h with no 24 h limit [75]. Subsequently, there were several reports of osmotic demyelination following treatment that remained within these boundaries [2]. Currently, the most commonly accepted limits are 10 mEq/L in any 24 h period and 18 mEq/L in any 48 h period [2, 12, 50, 55, 76]. These values were derived from observational studies of patients with severe hyponatremia and from reported cases of osmotic demyelination. It should be emphasized that these are limits not to be exceeded and not therapeutic goals.

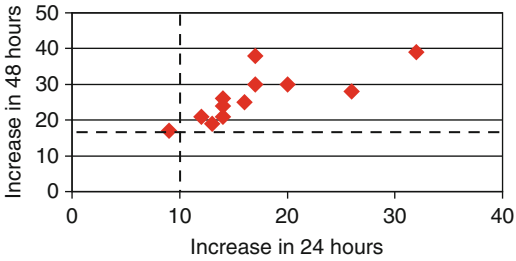

Fig. 12.5 Literature review of reported cases of osmotic demyelination syndrome in which data on the rate of correction in the first 24 and 48 h were provided [77]

While the vast majority of patients with osmotic demyelination have exceeded these limits, there are a few case reports of exceptions, particularly in patients with advanced liver disease.

In 1994, Lohr reviewed published cases of osmotic demyelination and noted a very high incidence of hypokalemia (66 of 74 patients with a plasma sodium $\leq$126 mEq/L and a documented plasma potassium value) [77]. In 20 of these cases, serial measurements of sodium and potassium were reported; in 95 % of cases, the increase in plasma sodium concentration exceeded 10 mEq/L/24 h and/or 18 mEq/L/48 h (Fig. 12.5).

A 1993 single center study of 14 patients with a delayed onset of neurological complications following treatment of severe hyponatremia (nine with CPM and/or EPM documented by brain imaging) found that while most patients had been corrected by >18 mEq/L/24 h, the complication was seen after correction by only 10 mEq/L/24 h and 21 mEq/L/48 h [61].

A study of all 255 patients with a plasma sodium <120 mEq/L admitted to a single hospital in Australia over a period of 7 years found no neurological complications among the 118 patients who were corrected by <12 mEq/L/day while 4 of 47 patients corrected by >12 mEq/L/day developed osmotic demyelination [72]. All four of the patients with ODS initially presented with a plasma sodium <105 mEq/L, all were hypokalemic, and three were alcoholic. Correction rates ranged from 14 to 25 mEq/L in 24 h and from 19 to 34 mEq/L in 48 h.

Unintended Overcorrection

A number of conditions temporarily or reversibly impair water excretion. Once the cause of water retention ends, excretion of dilute urine increases the plasma sodium concentration by much more than the clinician intends or expects [78–82]. There are several settings that can result in unintended overcorrection (1) volume resuscitation in patients with excess vasopressin due to hypovolemia or low solute intakes (e.g., beer potomania); (2) discontinuation of thiazide diuretics; (3) hormone replacement in patients with adrenal insufficiency; (4) spontaneous resolution of a reversible cause of the syndrome of inappropriate antidiuresis (SIADH), such as nausea, hypoxia, or recent surgery; (5) discontinuation of medications that cause

Table 12.1 Causes of unintentional overcorrection of hyponatremia

Cause of hyponatremia	Mechanism of overcorrection
Hypovolemia	Elimination of stimulus for vasopressin secretion with correction of volume deficit
Beer potomania, tea and toast diet	Enhanced delivery of glomerular filtrate to diluting sites with increased solute intake
Thiazide diuretics	Restored ability to maximally dilute the urine with discontinuation of diuretic
SSRI	Resolution of drug-induced SIADH
Desmopressin	Resolution of drug-induced SIADH
Hypopituitarism	Restored suppression of vasopressin secretion with cortisol replacement
Addison's disease	Reduced vasopressin levels with volume repletion and cortisol replacement
Hypoxemia	Removal of non-osmotic stimulus for vasopressin secretion with correction of hypoxemia
Nausea, surgery, pain, or stress	Spontaneous resolution of transient SIADH

SIADH (Table 12.1). In these settings, the urine may become maximally dilute, and the resulting water diuresis can increase the plasma sodium concentration by 2 mEq/L/h or more.

A single center retrospective study of 62 consecutive hyponatremic patients treated with hypertonic saline showed that unintended overcorrection of hyponatremia is disturbingly common [80]. In an attempt to maintain correction rates within therapeutic guidelines, these patients were given hypertonic saline at a relatively slow rate averaging less than 25 mL/h, and, despite frequent downward adjustments in the infusion rate, and/or administration of D5W as an "antidote," correction exceeded 12 mEq/L within 24 h in 11 % of cases, and in 10 % of cases it exceeded 18 mEq/L in 48 h. The magnitude of correction was directly correlated with the plasma sodium concentration, with more severe hyponatremia associated with more rapid correction (Fig. 12.6). With a plasma sodium $<$120 mEq/L, 74 % of patients experienced an increase in plasma sodium exceeding the increase that would have been predicted by the popular Adrogue–Madias formula [83, 84]; actual correction was as much as five times the predicted increase (Fig. 12.7). The formula assumes that saline is infused into closed system and does not take urinary losses into account. In fact, many patients developed a water diuresis during the course of therapy. Unintentional overcorrection of hyponatremia is not unique to hypertonic saline therapy; it may complicate any form of treatment for hyponatremia, including isotonic saline [82], vasopressin antagonists [85, 86] (Fig. 12.8), and urea [87].

Chronically hyponatremic patients who are potassium depleted are especially vulnerable to overcorrection. The plasma sodium concentration is a function of the ratio of exchangeable body sodium plus potassium divided by total body water; therefore potassium replacement increases the plasma sodium concentration [2, 88].

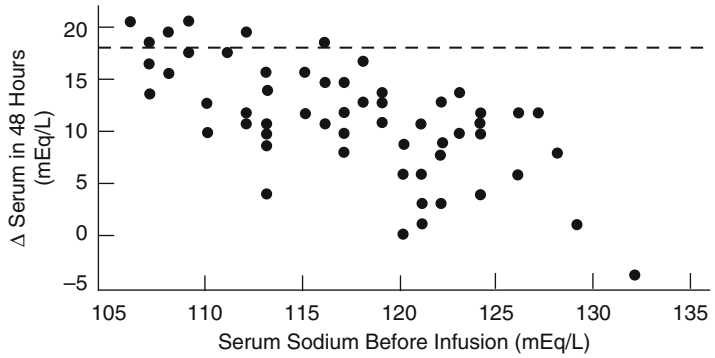

Fig. 12.6 Unintentional overcorrection of hyponatremia (>18 mEq/L in 48 h) among patients with serum sodium levels <120 mEq/L treated with 3 % NaCl in a single community teaching hospital; lower pretreatment serum sodium levels were significantly associated with larger increases in the serum sodium concentration [80] (with permission from CJASN)

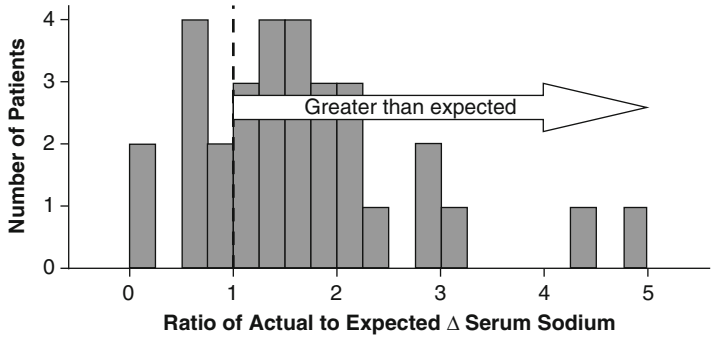

Fig. 12.7 The actual increase in serum sodium concentration after infusion of 3 % saline exceeded the increase predicted by popular formulas in most patients with serum sodium levels <120 mEq/L (see Fig. 12.7). The *dotted line* indicates that the actual increase and predicted increase are equal and for bars to the right of the *dotted line*, the actual increase exceeds the predicted increase [80] (with permission from CJASN)

A recent case report describes a patient with a plasma sodium of 96 mEq/L and a plasma potassium of 1.6 mEq/L who developed ODS following overcorrection of hyponatremia primarily attributable to replacement of the large potassium deficit [50]. It may seem paradoxical that potassium administration would result in ODS, because provision of an intracellular ion might be expected to protect against dehydration of brain cells. However, although potassium moves rapidly into skeletal muscle cells, it does not readily cross the blood brain barrier; thus, the most important effect from the brain's perspective is the rise in serum sodium concentration.

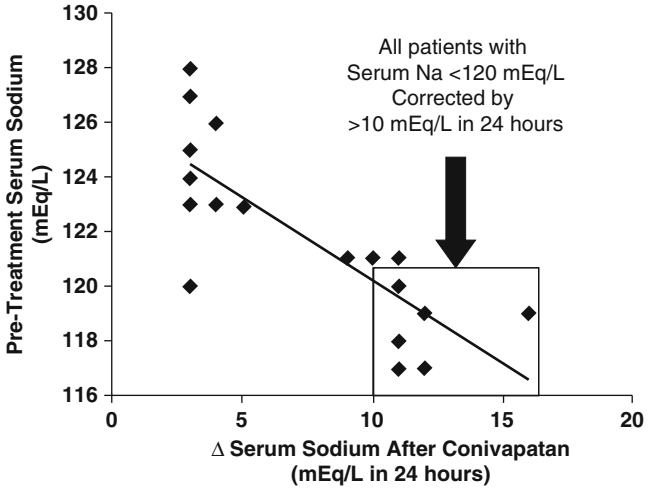

Fig. 12.8 Unintentional overcorrection of hyponatremia after treatment with the vasopressin antagonist, conivaptan; lower pretreatment serum sodium levels were significantly associated with larger increases in the serum sodium concentration and in all patients with pre treatment levels <120 mEq/L, correction exceeded 10 mEq/L in 24 h [85] (by permission of Oxford University Press)

Therapeutic Re-lowering of the Plasma Sodium

In animal models, both the incidence and severity of brain damage caused by rapid correction of hyponatremia are reduced by therapeutically re-lowering the plasma sodium concentration [51]. In a few case reports, the same strategy has been used successfully in humans, reversing early symptoms of ODS that had developed following unintentional rapid correction of chronic hyponatremia [2, 55, 89–91] (Fig. 12.9).

Desmopressin has also been used in the management of chronically hyponatremic patients at risk for ODS without waiting for the symptoms of ODS to develop [92]. If the plasma sodium concentration is increasing too rapidly, the drug can be given to halt a water diuresis, so as to prevent overcorrection from occurring. In the authors' experience, stopping water losses with desmopressin is less labor-intensive and more reliable than attempts to match urinary water losses with 5 % dextrose in water. If the increase in plasma sodium concentration has already exceeded therapeutic limits, desmopressin can prevent further water losses and make it easier to re-lower the plasma sodium concentration. In a single center series, 11 patients were treated concurrently with desmopressin acetate and 5 % dextrose in water, re-lowering the plasma sodium by 2–9 mEq/L; there were no serious adverse consequences, and all patients survived without neurological sequelae [92].

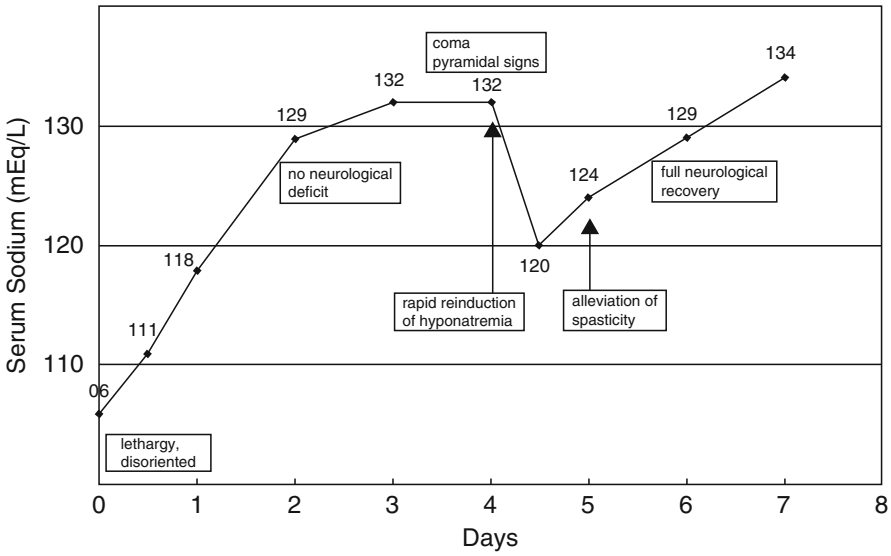

Fig. 12.9 Therapeutic re-lowering of the serum sodium concentration. After neurological features of ODS developed 2 days following unintentional overcorrection (23 mEq/L in 48 h) of severe hyponatremia (serum sodium 106 mEq/L), the patient was given desmopressin and 5 % dextrose in water, lowering the serum sodium concentration by 12 mEq/L, from 132 to 120 mEq/L. Neurological abnormalities resolved after this therapy [90] (with permission of Wolters Kluwer Health)

When desmopressin is used to treat diabetes insipidus, it is given once or twice daily. The goal in diabetes insipidus is to avoid iatrogenic hyponatremia by allowing partial escape from antidiuresis. When the drug is used to manage overcorrection of hyponatremia, the goal is different. In this case, escape from antidiuresis is undesirable as it can lead to overcorrection of hyponatremia; therefore, desmopressin is given at 6–8 h intervals. Once the rate of correction has been slowed or stopped by regular doses of desmopressin, correction of hyponatremia can resume, slowly increasing the plasma sodium with the concurrent administration of 3 % saline.

Controlled Correction with Concurrent 3 % Saline and Desmopressin

More recently, a more proactive strategy using desmopressin routinely in the treatment of hyponatremia has been proposed (Fig. 12.10, Table 12.2). Rather than giving desmopressin to stop a water diuresis after it has already begun, desmopressin is given at the start of therapy along with 3 % saline in order to achieve a more controlled rate of correction. The administered desmopressin

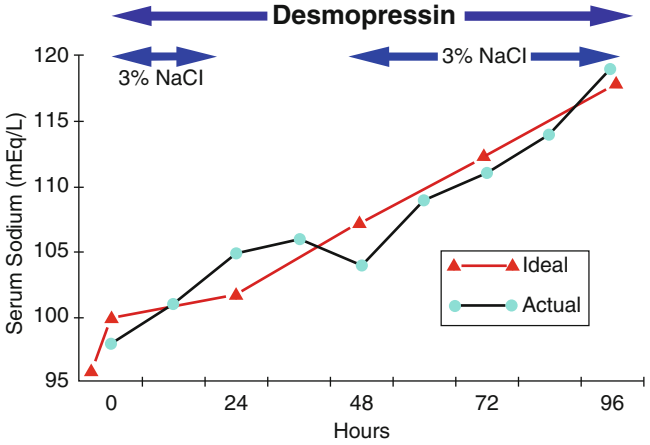

Fig. 12.10 Combined treatment with 3 % saline and desmopressin. Controlled correction of hyponatremia in a patient with a pretreatment serum sodium concentration of 96 mEq/L is illustrated. Desmopressin was begun concurrently with 3 % saline and was continued at for the next several days. The rate of hypertonic saline infusion was titrated to achieve the desired increase in serum sodium concentration—an initial increase of 4 mEq/L in the first few hours with an overall correction rate of 6 mEq/L/day [94] (reprinted with permission from Elsevier)

Table 12.2 Protocol for controlled correction of severe hyponatremia using intravenous hypertonic saline and desmopressin

- DDAVP (start immediately without waiting for 3 % saline)
  - 2 mcg subcutaneously every 8 h
  - Continue until serum Na >126 mEq/L
- Concurrent 3 % saline (obtain serum sodium before starting)
  - For severe symptoms
    - 1–2 mL/kg/h for up to 3 h or
    - 100 mL bolus, repeated every 10 min if needed × 2
  - For mild to moderate symptoms
    - Initial dose: 0.3 mL/kg/h
    - Adjust rate to achieve target based on serum sodium
    - Discontinue infusion when daily target reached and resume the next day
- Potassium replacement
  - To raise the serum sodium
    - 20 mEq in 50 mL water (400 mM) KCl substitutes for 40 mL 3 % saline
  - To keep the serum sodium constant
    - 10 mEq in 100 mL water (100 mM) KCl
- Monitoring of serum sodium
  - Immediately after bolus or rapid infusion of 3 % saline for severe symptoms
  - 4 h after starting 3 % saline or after change in infusion rate
  - Every 6 h after response to 3 % saline established
- Target
  - 6 mEq/L within first 6 h for severe symptoms
  - 6 mEq/L every 24 h in all cases

creates a state of iatrogenic SIADH, making urinary water losses a fixed variable that contributes little to the increase in serum sodium concentration [93]. Hypertonic saline is given along with desmopressin until the serum sodium has been increased above 126 mEq/L. Desmopressin and hypertonic saline are then discontinued and the patient's serum sodium concentration returns to normal because of urinary water losses that eventually increase. The authors now use this regimen for most patients with a plasma sodium concentration <120 mEq/L.

Desmopressin is not recommended for patients who are unable or unwilling to curtail their water intake, and it is probably unnecessary in patients with SIADH due to small cell lung cancer or brain tumor (where there is little likelihood of a reversible cause for water retention). Desmopressin is given in a dose of 2 mcg subcutaneously or intravenously every 6–8 h, and the rate of 3 % saline infusion is tailored to the severity of the patient's presenting symptoms. Bolus 3 % saline can be given for the most severe symptoms while a slow infusion (0.3 mL/kg body weight) is used when symptoms are mild. In potassium-depleted patients 400 mM KCl (20 mEq in 50 mL water) can be substituted for 3 % saline to raise the serum sodium and 100 mM KCl (10 mEq in 100 mL water) is used to replace potassium without increasing the serum sodium (Table 12.2).

Therapeutic Targets

If a 4–6 mEq/L increase in serum sodium concentration is "enough" to improve the most severe symptoms in patients with acute hyponatremia, then a therapeutic goal of 6 mEq/L/day is reasonable in chronically hyponatremic patients, even those with extremely low serum sodium concentrations. Setting the target at 6 mEq/L/day is sufficiently removed from therapeutic limits to allow room for error. This recommendation translates to an easy to remember "rule of sixes": "Six a day makes sense for safety; so give six in six hours for severe sx's and stop" [94]. In other words, for all patients the therapeutic goal is correction by 6 mEq/L/day. For patients with severe symptoms, the day's correction is frontloaded in the first 6 h and correction is then postponed until the next day when it is resumed at a rate of 6 mEq/L/day.

Therapeutic Recommendations for Severe, Symptomatic Hyponatremia

Fluid Restriction

Unless the urine is maximally dilute, hyponatremic patients should be fluid restricted. However, fluid restriction alone will increase the plasma sodium concentration by little more than 1–2 mEq/L/day unless the cause of water retention is

reversible, so that urinary water losses increase. The concentration of cations in the urine divided by the plasma sodium concentration can help predict the response to water restriction [95]. A ratio <0.5 means that more than half the urine is electrolyte-free water; in this case, correction will be prompt, often faster than intended, and fluid restriction can be relaxed. A ratio >1.0 means that the urine contains no electrolyte-free water; in this case water intake must be severely restricted or, alternatively, the concentration of urinary electrolytes can be reduced with furosemide, or hypertonic saline can be given.

Hypertonic Saline

We recommend giving a short, but limited infusion of 3 % saline to all hyponatremic patients with neurological symptoms. Patients with seizures or coma and symptomatic patients with acute postoperative hyponatremia or self-induced water intoxication should be given a 100 mL bolus of 3 % saline, with two additional doses administered every 10–15 min if the patient's condition has not yet improved. We also recommend treating all hyponatremic patients with intracranial pathology with hypertonic saline.

Hypertonic saline has been combined with furosemide to rapidly increase the serum sodium concentration [33, 96]. The combination is theoretically attractive because furosemide blocks sodium reabsorption in the ascending limb, thereby decreasing the concentration gradient in the renal medulla and increasing free water excretion in the urine. However, we do not recommend the routine use of this regimen for three reasons (a) the diuretic decreases intravascular volume which may compromise an already impaired cerebral circulation; (b) the combination of saline infusion and furosemide results in potassium depletion; (c) use of the diuretic makes the increase from 3 % saline less predictable.

Potassium

Administration of potassium will help increase the plasma sodium concentration in patients with coexistent hypokalemia. As shown in (12.1), above, the plasma sodium concentration is a function of exchangeable cations divided by total body water; therefore, each mEq of potassium added to the body can be expected to increase the plasma sodium concentration by as much as a mEq of sodium. Potassium is available commercially in the USA as a 100 mM or a 400 mM solution in water. Administration of 50 mL/h of the latter solution (20 mEq/h) is equivalent to the administration of 3 % NaCl at 40 mL/h.

Isotonic Saline

Isotonic saline corrects hyponatremia caused by volume depletion because elimination of a volume stimulus for vasopressin secretion results in a water diuresis. However, if vasopressin is secreted for another reason (e.g., SIADH caused by tumors, neurological conditions, or medications), isotonic saline will be ineffective. In fact, as previously discussed, the plasma sodium concentration may actually *decrease* during the infusion of isotonic saline if the urine cation concentration greatly exceeds 154 mEq/L (see Fig. 12.1) [6]. Therefore, isotonic saline should be reserved for patients who require volume resuscitation for hypotension or for mildly hyponatremic patients who are unlikely to be harmed if the plasma sodium level fails to improve with this therapy.

Desmopressin

Many hospitalized patients present with multiple conditions that are potential causes for hyponatremia. Although urine chemistries can help predict the response to isotonic saline or water restriction, these results are not always available. Initiation of therapy with hypertonic saline will reliably increase the plasma sodium concentration regardless of etiology. An infusion of 3 % saline at 15–30 mL/h can be used for chronically hyponatremic patients with mild symptoms, continuing until the plasma sodium has increased by 4–6 mEq/L. Because there is often a risk that an unexpected water diuresis may emerge during therapy, we recommend administration of desmopressin in most patients to make the response to hypertonic saline more predictable. Chemistries should be obtained at 4–6 h intervals and the urine output should be carefully monitored. Hypertonic saline should be discontinued if a water diuresis emerges.

Vasopressin Antagonists

The place of vasopressin antagonists (vaptans) in the treatment of symptomatic or acute hyponatremia is not yet well established. These agents are often effective, and they make physiological sense as they address the primary disturbance in most cases of hyponatremia: water retention. However, some patients fail to respond to recommended doses of the vaptans with increased water excretion [85]. For this reason, we cannot recommend that these agents be used to treat acutely symptomatic patients.

Hemodialysis

Patients with oliguric kidney failure often develop hyponatremia; the serum sodium concentration can be expected to increase rapidly if the patient is treated with conventional hemodialysis. In experimental models, uremic animals are less likely to develop osmotic demyelination after rapid correction of hyponatremia than animals without kidney failure. In addition, dehydration of brain cells caused by a rising serum sodium concentration during dialysis would be expected to be countered by brain swelling caused by a falling BUN. Although there is a clinical impression that uremic patients with hyponatremia seem to tolerate rapid increases in the serum sodium concentration, there have been a few case reports of ODS complicating hemodialysis. Therefore, large increases in the serum sodium during dialysis should be avoided if possible. Because dialysate sodium concentrations cannot be reduced below 130 mEq/L with available equipment, blood flow should be markedly reduced (to approximately 1 mL/kg body weight per minute), and dialysis time should be shortened if the serum sodium is <120 mEq/L. If one assumes 100 % equilibration of sodium between the dialysate (130 mEq/L) and the patient's blood at the initiation of dialysis, the amount of sodium transferred to the patient will equal the blood flow in liters per hour multiplied by the difference between plasma and dialysate sodium concentrations. These assumptions were validated in a recent case report of a 50 kg elderly woman with a serum sodium concentration of 113 mEq/L who was dialyzed against a 130 mEq/L sodium bath for 3 h at a blood flow rate of 50 mL/min (3 L/h or 9 L in a 3 h session), using the pediatric mode of the dialysis machine [97]. The serum sodium concentration increased by 6 mEq/L during dialysis, matching the authors' predictions (based on total body water of 25 L):

$$\text{Sodium transferred to patient} = (130 - 113)\text{mEq/L} \times 9\ \text{L} = 153\ \text{mEq}$$

$$\text{Predicted } \Delta \text{ serum Na} = 153\ \text{mEq}/25\ \text{Liters} = 6\ \text{mEq/L}.$$

For patients with extremely low serum sodium concentrations, a form of continuous renal replacement therapy can be used. In this case, sodium concentration of the replacement fluid or dialysate can be adjusted to be a few mEq/L higher than the patient's serum sodium concentration.

Treatment of Hyponatremia in Intracranial Disease

Hyponatremia in patients with intracranial pathology is often attributed to "cerebral salt wasting," particularly in the critical care and neurosurgery literature [10]. It is difficult to distinguish between SIADH and salt wasting. A diagnosis of "salt wasting" requires proof that the patient is losing salt in the urine despite hypovolemia. Unfortunately, there is no gold standard to define volume depletion, because a decreased effective arterial blood volume is a concept and not a

Table 12.3 Standardized hypertonic saline protocol for patients with acute neurological disorders [100]

Serum sodium	Δ Infusion rate
<130 mEq/L	Increase by 20 mL/h to maximum 80 mL/h
130–135 mEq/L	Increase by 10 mL/h to maximum 80 mL/h
136–140 mEq/L	No change
>140 mEq/L	Hold and resume when in therapeutic range

Sliding scale hypertonic saline protocol
3 g NaCl po or by NG tube q6h plus
3 % NaCl IV starting at 20 mL/h, adjusted per sliding scale based on q 6 h serum sodium values

measurable variable; in fact, we often use a low urine sodium as one of the criteria to diagnose hypovolemia. Measurements of plasma volume or fluid balance are ambiguous because vasoconstriction due to increased catecholamines may reduce the absolute plasma volume, by reducing the large fraction normally residing in venous capacitance vessels and by increasing blood pressure. Thus, urinary sodium excretion may be a physiological response to a "filled" arterial blood volume rather than true salt wasting. Furthermore, the distinction between SIADH and salt wasting may not be relevant therapeutically. If hypovolemia were the cause of increased ADH levels in patients with subarachnoid hemorrhage or other acute neurological conditions, then volume replacement would result in suppression of ADH secretion and autocorrection of hyponatremia due to the elimination of excess water in the urine. There is no evidence that such a sequence commonly occurs. In a prospective cohort study, Diringer et al. showed that while administration of isotonic saline prevented hypovolemia in patients with subarachnoid hemorrhage, it did not suppress ADH secretion or prevent hyponatremia from occurring [9].

Patients with intracranial pathology are at high risk of herniation if nondiseased brain is allowed to swell [98]. Therefore, treatment strategies must be designed to reliably increase the plasma sodium concentration. Fluid restriction is ineffective in preventing a fall in plasma sodium concentration if the patient is excreting concentrated salt in the urine. Furthermore, fluid restriction risks impairing cerebral perfusion and has been associated with worse neurological outcomes [99]. Therefore, whether one believes that high urine sodium levels are due to SIADH or to salt wasting, the most reliable way to prevent the plasma sodium concentration from falling is to administer sodium solutions that are higher in concentration than the urine [10].

Urine sodium concentrations do not usually exceed 250 mEq/L. Therefore, administration of 1.5 % saline to patients with intracranial pathology who require volume expansion will usually prevent the plasma sodium concentration from falling. Alternatively, a sliding scale has been used in this setting, using intermittent infusions of 3 % saline and administration of salt tablets [1] (Table 12.3). Some investigators have reported that administration of mineralocorticoids and steroids is also effective in preventing or treating hyponatremia in patients with subarachnoid hemorrhage [101, 102]; however, given the side effects, we do not see an advantage over the administration of concentrated sodium solutions.

Treatment of Mild Asymptomatic Hyponatremia

There is increasing evidence that mild chronic hyponatremia is not benign [103]. Mild, apparently asymptomatic hyponatremia causes gait disturbances and increases the risk of falls [104]. Falls often result in fractures [105, 106], possibly because hyponatremia is a cause of osteoporosis [107]. Mild hyponatremia adversely effects cognitive ability and mental health [104].

Oral vaptans have been shown to maintain normonatremia in ambulatory patients with chronic hyponatremia [108]. However, the cost of such therapy is currently prohibitive and proof that it improves the adverse outcomes associated with hyponatremia is needed before chronic vaptan therapy can be recommended for all hyponatremic patients. Unfortunately, there are few well-tested alternatives. Demeclocycline, a tetracycline antibiotic that causes nephrogenic diabetes insipidus as a side effect, was commonly used to treat hyponatremia prior to the introduction of vaptans; the agent has many disadvantages (a) it causes photosensitivity; (b) it is nephrotoxic, especially in patients with heart failure and liver disease; (c) it can cause superinfection with *C. difficile*; (d) its effect on water excretion is delayed for several days, and it continues to act for several days after the drug is discontinued [76]. Urea has been used extensively in Belgium to treat both acute and chronic hyponatremia caused by SIADH [87, 109–111], heart failure [112], and cirrhosis [113]; urea increases urinary free-water losses in patients with vasopressin-mediated hyponatremia by reducing the electrolyte concentration of the urine. A recent single-center prospective open label trial of patients with chronic SIADH found that urea therapy was as effective in controlling the serum sodium concentration and was as well tolerated as prior therapy with vaptans [114]. Salt tablets combined with lasix have reported to be successful in managing chronic SIADH in a small number of ambulatory patients [113].

Hyponatremia in Edematous Conditions

Hyponatremia is associated with poor outcomes in both heart failure and liver disease, but it is not known whether mortality rates can be improved by correcting the electrolyte disturbance [115, 116]. Fluid restriction and loop diuretics are the mainstay of treatment, but these measures are relatively ineffective [117, 118]. There is an obvious reluctance to treat edematous patients with hypertonic saline because this will increase the severity of edema. Interestingly, however, published experience using 3 % saline combined with high doses of loop diuretics indicates that this therapy is surprisingly well tolerated in patients with advanced heart failure and actually improves outcomes when compared to treatment with high dose diuretics alone [119, 120].

Vaptans are the best available treatment for hyponatremia in edematous patients with cirrhosis and heart failure, and they are effective in increasing the serum sodium

concentration in both disorders [121–123]. However, patients with these conditions often have far advanced disease, and their hyponatremia is likely to recur when vaptan therapy is discontinued. The benefit of raising the serum sodium concentration and maintaining normonatremia with chronic therapy may not justify the cost. A multicenter trial found no mortality benefit of long-term therapy with tolvaptan in patients with heart failure [124]. The most compelling case for vaptan therapy is in hyponatremic patients awaiting liver transplantation. Normalizing the serum sodium concentration in the short term prior to surgery may help avoid iatrogenic injury caused by a sudden perioperative increase in serum sodium concentration.

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