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REVIEW ARTICLE

Hyponatremia and the syndrome of inappropriate secretion of antidiuretic hormone (SIADH)

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ABSTRACT. The syndrome of inappropriate ADH secretion (SIADH), also recently referred to as the "syndrome of inappropriate antidiuresis", is an often underdiagnosed cause of hypotonic hyponatremia, resulting for instance from ectopic release of ADH in lung cancer or as a side-effect of various drugs. In SIADH, hyponatremia results from a pure disorder of water handling by the kidney, whereas external Na^+ balance is usually well regulated. Despite increased total body water, only minor changes of urine output and modest edema are usually seen. Renal function and acid-base balance are often preserved, while neurological impairment may range from subclinical to life-threatening. Hypouricemia is a distinguishing feature. The major causes and clinical variants of SIADH are reviewed, with particular emphasis on iatrogenic complications and hospital-acquired hyponatremia. Effective treatment of SIADH with water restriction, aquaretics, or hypertonic saline + loop diuretics, as opposed to worsening of hyponatremia during parenteral isotonic fluid administration, underscores the importance of an early accurate diagnosis and careful follow-up of these patients.
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INTRODUCTION

The syndrome of inappropriate ADH secretion (SIADH) results from a dysregulated release of ADH (or AVP), a cyclic nonapeptide released by the neurohypophysis, which promotes H_2O reabsorption in the distal nephron. Mild and asymptomatic forms are rather common in hospital settings (1-4). Among other neurological abnormalities, hyponatremia is believed to be responsible for attention deficits, gait and falls, significant causes of hospitalization in the elderly (4, 5). More profound hyponatremia may be associated with variable degrees of motor and cognitive impairment, occasionally leading to fatal outcomes. A typical feature of SIADH is preserved renal handling of Na^+ despite a severely impaired free H_2O clearance (Table 1) (1-3, 6, 7).

Under physiologic conditions, ADH release is suppressed when plasma osmolality decreases below 275 mOsm/kg, which roughly corresponds to a plasma concentration of Na^+<135 mEq/l (3, 6-9). In typical SIADH, dysregulated synthesis or release of ADH promotes H_2O reabsorption with ensuing hemodilution and increased total body H_2O (TBW) (3, 6-9). Obviously, H_2O intake is a critical step leading to the onset of hyponatremia during SIADH, as H_2O restriction effectively counteracts the decrease of plasma Na^+ (6-9). Fluid administration during hospital admissions or in nursing homes is likely responsible of a large number of cases of hyponatremia in individuals with inappropriately high ADH levels for whatever reason (4). Current figures indicate mild hyponatremia (Na^+ 130-134 mEq/l) as an acquired finding in 15-20% of all hospitalized patients, with moderate to severe hyponatremia (Na^+<130 mEq/l) occuring in 1-7% of them. In this latter group, most cases are SIADH (1-4).

Key-words: Antidiuretic hormone (ADH), arginine vasopressin (AVP), hyponatremia, plasma osmolality, syndrome of inappropriate ADH release (SIADH).

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PHYSIOLOGY OF THE ADH/AVP SYSTEM

Structure and synthesis of ADH

ADH/AVP is a 9-aa. cyclic polypeptide stretch (Cys-Tyr-Phe-Gln-Asn-Cys-Pro-Arg-Gly) with a disulphide bridge linking the two cysteines and a MW of 10 KDa, derived from a pre-pro-hormone precursor of 164 aa., synthesized by neurons of the magnicellular nucleus of the anterior hypothalamus. Pre-pro-ADH is subsequently activated through sequential cleavage of 3 peptides (neurophysin II, a glycopeptide, and a signal peptide) (10, 11). The encoding genes are 3, comprised of about 15 Kb on chromosome 20. Exon 1 encodes for the proper ADH sequence, the signal peptide, and a Gly-Lys-Arg cleavage site. Exon 2 encodes for neurophysin II, while exon 3 encodes a glycopeptide linked to neurophysin *via* an Arg residue (10, 11). Secretion granules are then transferred across the supraoptic-parahypophyseal tract into the posterior lobe of the pituitary. A certain fraction of the granules directly enters the cerebrospinal fluid and/or portal capillaries. This phenomenon explains why lesions of the posterior pituitary or the supraoptic-hypophyseal tract do not always result in complete *diabetes insipidus* (DI). On the other hand, sudden release of secretory granules upon ischemia or necrosis of this region (e.g., stroke, neoplasms or local injury) accounts for the often observed, transient SIADH phase followed within days by DI in patients with destructive injury of the posterior *sella turcica*.

Table 1 - *Calculation of the free water clearance (C_{H_2O}).*

$V_{(urine\ flow,\ vol/min)} = C_{osm} + C_{H_2O}$

$- C_{H_2O} = V - C_{osm}$

$- C = \frac{U \times V}{P}$

$- C_{osm} = \frac{U_{osm} \times V}{P_{osm}}$

$- C_{H_2O} = V - \frac{(U_{osm} \times V)}{P_{osm}}$

Example: with a urine flow of 4 ml/min $\quad 4 - \frac{(140 \times 4)}{280} = 2$ ml/min

C_{H_2O} = 0 urine isotonic *vs* plasma (280 mOsm/kg)
>0 diluted urine
<0 concentrated urine (in response to ADH)

Legend
V = urine flow/min is the sum of clearances I of osmolytes (C_{osm}, urea, Na^+, K^+, Cl^-, Ca^{2+}, urate, phosphates, sulphates, *etc.*) and free water (C_{H_2O})
U = urine, P = plasma
$C = \frac{U \times V}{P}$ is the general formula of all renal clearances

Role of receptors of ADH

The main physiologic role of ADH is to control the homeostasis of body fluids, through a mechanism of neurosecretion coupled to the thirst-control brainstem center. ADH is rapidly cleared by the liver and the kidney through detachment of the glycinoamidic end, with an average half-life of 15-20 min. Its plasma levels are between 1.5 and 6 ng/l, with a peak in the early morning hours, and a steady decrease thereafter, as a function of fluid and food intake. Some 25-90 ng ADH are excreted in the urine over 24 h (11-13).

Two major classes of ADH receptors have been reported thus far, labeled as V_1 and V_2. The first group consists of high-affinity, fairly ubiquitous vasoconstrictor receptors coupled to a phosphoinositide breakdown signal transduction cascade, relying upon a sharp rise of cytosolic free Ca^{2+} ($[Ca^{2+}]_i$) (11-13). Parallel release of 1.2-diacylglycerol in combination with raised $[Ca^{2+}]_i$ activates protein kinase C isoforms, resulting in the phosphorylation of specific substrates in the liver, vascular smooth muscle cells (including glomerular mesangial cells), uterus, male reproductive tract, Leydig cells of the testis, lymphocytes, platelets, and neurons in the brainstem. In the hypophysis, a V_1 subtype, V_{1b}, has been described, with a lower binding constant for selective antagonists (11-13).

V_2 receptors differ from the vasoconstrictor binding site for their signal transduction mechanism, coupled to adenylate cyclase III and VI through heterotrimeric G_s proteins, as well as their selective expression on tubular cells of the distal nephron, namely the normally water-impermeant collecting duct (13). These receptors have a conventional 7-transmembrane spanning domain structure, with a cytosolic COOH-terminus and an outer plasma membrane NH_2-terminus. Binding to the V_2 receptor promotes the formation of intracellular cAMP, which in turn activates protein kinase A (PKA). Among the phosphorylated targets of PKA, inducible aquaporin-2 (AQP-2) is translocated from the cytosol to the luminal surface of epithelial cells by a process of exocytosis, by which tetrameric channels are assembled into the plasma membrane, yielding transcellular H_2O flow from the urine to the cytosol (14-19). It appears that AQP-2 is also transcriptionally upregulated during settings of prolonged hyperosmolality and antidiuresis. Constitutive AQP-3 and -4 expressed on the basolateral surface of cells provide the driving force for net H_2O efflux towards the hyperosmotic deep medullary interstitium (18-21).

Upon clearance of ADH from the receptors, AQP-2 is quickly internalized and recycled within the cytosol, rendering the collecting duct again water-impermeant (18-21). ADH neurosecretion is controlled by hypothalamic osmoreceptors, whose task is to keep plasma osmolality within a very narrow range of 290±5 mOsm/kg (22-24). The so-called "reset osmostat" syndrome is a parallel disorder to the SIADH, whereby the sensing apparatus reads osmolalities of 260-270 mOsm/kg as normal, with resulting "benign" hyponatremia characterized by normal handling of an oral H_2O load, as opposed to substantial H_2O retention in SIADH (24-26, see below). A further level of osmolality control is enacted by stretch sensors in the left atrium, as well as aortic and carotid baroreceptors (21, 23). Other neurotransmitters and neuropeptides have direct effects on the hypothalamus. Acetylcholine, angiotensin II, and histamine are activators, while norepinephrine, dopamine, and prostaglandins are both stimulatory and inhibitory. γ-aminobutyric acid is a pure inhibitor (27).

ADH and plasma osmolality

H_2O excretion and reabsorption occur passively *via* constitutive AQP-1 in the proximal tubule and the descending loop of Henle (Pf ~ 3×10^9 H_2O molecules per subunit/sec), down an osmotic gradient generated by NaCl transport, thus keeping constant the extracellular fluid volume. The kidney participates in the control of plasma osmolality through excretion or reabsorption of free H_2O. Such function is mediated by ADH in the distal tubule. In its presence, H_2O is reabsorbed and hypertonic urine is produced, while in its absence H_2O is excreted in hypotonic urine resulting from a positive free H_2O clearance (21, 23) (Table 1). Urine osmolality roughly reflects the ability of the kidney to produce diluted or concentrated urine, although it is not an accurate estimate of the H_2O clearance, which should rather be calculated by means of the formula in Table 1. The excretion of a large volume of diluted urine is considered appropriate if it follows a H_2O load, or inappropriate if resulting from a defect of ADH release (central DI) or from renal insensitivity to the hormone. In turn, this may be related to defects of the V_2 receptors, AQP-2 or both, in the so-called "nephrogenic" DI. In both cases, loss of solute-free H_2O leads to a rise of plasma osmolality, unless free H_2O is simultaneously administered.

PATHOPHYSIOLOGY OF SIADH

In patients with SIADH, 4 major patterns of polypeptide secretion can be distinguished (3) (Table 2). In type A, occurring in 40-70% of patients, a random pattern of hor-

Table 2 - *Pathophysiology and main subtypes of syndrome of inappropriate ADH secretion.*

- Type A (40-70% of cases): "random" ADH release, independent of plasma osmolality.
- Type B (20-40%): "reset osmostat". ADH neurosecretion driven by plasma Na^+ levels of 125-130 mEq/l, perceived as "normal".
- Type C (10%): ADH not suppressed by a H_2O or iv water load.
- Type D (<5%): normal ADH release but lower receptor threshold.

mone secretion is usually observed, as in the case of ADH-secreting neoplasms. Type B is slightly less common, accounting approximately for 20-40% of all SIADH cases. Type B is the classic "reset osmostat" syndrome, whereby a Na^+ concentration of 125-130 mEq/l is perceived as normal (26). Above this threshold, ADH release occurs, preventing achievement of physiologic Na^+ levels of 140-145 mEq/l. In "reset osmostat" patients, administration of an oral H_2O load results in a normal excretion of >80% within 4 h (see below). The "reset osmostat" syndrome is usually seen in elderly patients as a result of pharmacologic agents, brainstem degenerative disorders, or chronic infections (such as tuberculosis), by yet unknown mechanisms (24-26). This is at variance with the "true", complete SIADH, in which H_2O is retained, with further worsening of hyponatremia. In the rare type C, ADH is not inhibited by an oral or iv H_2O load. A hypothalamic dysfunction with low-grade, steady dysregulated ADH synthesis is likely involved. Type D is a very rare condition, characterized by normal/low levels of ADH, while receptor sensitivity is apparently increased (3). The demonstration of the presence of gain-of-function mutations of the V_2 receptor gene led to the proposal to rename SIADH as "syndrome of inappropriate antidiuresis (SIAD)", in order to include also these SIADH-like clinical conditions, yet with undetectable ADH levels (28, 29).

Causes of SIADH

These 4 pathophysiological categories do not closely match the known causes of SIADH, listed in detail in Table 3. Neuropsychic alterations can stimulate ADH release more or less directly, by activating cortical neurons, which in turn activate the hypothalamus (30-33). Psychogenic polydipsia, i.e. uncontrolled drinking behavior, can contribute to or mimic SIADH, particularly in settings of reduced renal function, favoring dilutional hyponatremia.

A vast array of drugs have an impact on ADH release and/or tubular handling of H_2O, acting centrally or at a more peripheral level. As an example, the alkylating agent cyclophosphamide may act both at the hypothalamic nuclei responsible for ADH neurosecretion, as well as on tumor cells responsible for cases of paraneoplastic polypeptide production (34-37). In the latter case, cell lysis is responsible for ADH release, in a fashion resembling the tumor lysis syndrome or an acute injury of the hypothalamic/neurohypophyseal area. At the same time, cyclophosphamide acts on the tubular epithelium, potentiating ADH-induced H_2O transport (34, 35). Its metabolites are also toxic for the bladder epithelium, leading in some instances to hemorrhagic cystitis. Oral H_2O loading, often prescribed to prevent urothelial injury, may thus aggravate hyponatremia, in the presence of elevated ADH levels (34-37).

A leading cause of SIADH is rapidly becoming the widespread use of antidepressants, particularly in elderly patients. Selective serotonin uptake inhibitors are frequently involved, with up to 32% of treated patients developing features of SIADH (38, 39) (Table 3). About 12% of in-hospital treated patients present with SIADH, particularly when simultaneously receiving neuroleptics or antidepressants, diuretics and iv fluid therapy (40).

Chlorpropamide is a glucose-lowering agent, occasionally found to decrease Na^+ levels by 4-6%, particularly when associated with thiazide diuretics. The mechanism of action may be receptor sensitization, leading to a group D-type tubular dysfunction (41-44). Non-steroidal anti-inflammatory drugs (NSAID) potentiate ADH by blocking prostaglandin synthesis, which physiologically antagonizes adenylate cyclase at the level of the collecting duct epithelium (45). H_2O retention

Table 3 - *Major known causes of syndrome of inappropriate ADH secretion.*

Increased hypothalamic/hypophyseal ADH release
Neurologic, neuropsychic disorders
- Infections (meningitis, encephalitis, sarcoidosis, abscesses, herpes virus infections, HIV)
- Vascular causes (thrombosis, subarachnoid/subdural hemorrhage, temporal arteritis)
- Psycosis
- Post-surgical causes
- Guillain-Barrè syndrome
Drugs:
- Antidepressants: carbamazepine, tryclic antidepressants, phenothiazines, haloperidol, serotonin uptake inhibitors, quinolones, leveteiracetam
- MDMA/"ecstasy"
- cyclophosphamide
- chlorpropamide
- non-steroidal anti-inflammatory drugs
Pulmonary disorders:
- tubercolosis, viral/bacterial pneumonia, asthma, atelectasia, pneumothorax, HIV
Ectopic production
Malignancies
- pulmonary microcitoma
- nasopharyngeal tumors
- GI/pancreatic malignancies
- GU tract malignancies
- Mesothelioma
- Lymphoma, sarcoma
Amplification of the effects of ADH at the receptors
Drugs: cyclophosphamide, chlorpropamide
Release of non-ADH antidiuretic peptides
Prolactinoma, Waldenström macroglobulinemia

MDMA: 3,4-Methylenedioxymethamphetamine; GI: gastrointestinal; GU: genitourinary.

and/or edema are not uncommon among patients treated with NSAID.
Pulmonary diseases are often associated with ADH disorders. Tuberculosis, viral or bacterial pneumonia, asthma, atelectasis, pneumothorax, all increase ADH levels *via* mechanisms incompletely understood, possibly related to decreased venous efflux with volume receptor activation (46-48). On the other hand, small cell lung carcinomas and other neoplasms are often associated with the SIADH through the paraneoplastic synthesis of ADH or its carrier, neurophysin (49-55) (Table 3).

CLINICAL PRESENTATION OF SIADH

Pseudohyponatremia

In the differential diagnosis of hyponatremias, SIADH should first be evaluated against pseudohyponatremia, resulting from laboratory artefacts in settings of severe hypertrigliceridemia or paraproteinemia with a narrowing of the plasma "H_2O space" (56-58). In such cases, direct concentration measurement by Na^+-sensing electrodes avoids the error associated with restriction of the "H_2O space" in flame photometry. Actual Na^+ can be obtained from the formula:
• measured Na^+ × 93 / % plasma H_2O
In turn, % plasma H_2O can be estimated as:
• 99-1.03 (plasma lipids, g/l) – 0.73 (plasma proteins, g/dl)
The opposite applies to decompensated diabetes mellitus, in which the osmotic attraction of glucose drives H_2O out of the cells, thus diluting Na^+ as a function of severity of hyperglicemia (59-61). The appropriate calculation of actual Na^+ is then:
• [0.016 (plasma glucose – 100)] + measured Na^+

Hypo- and eu-/hypervolemic hyponatremia

SIADH patients typically present with hypotonic hyponatremia, i.e., plasma osmolality below 280 mOsm/kg. The clinical picture of hyponatremia ranges from hypovolemic patients (that is, hypotensive, tachycardic, volume-depleted, with greater $TBNa^+$ depletion than TBW), to euvolemic or hypervolemic (61-63). The latter subset is volume-expanded, with hypertension and/or edema, and an actual increase of TBW over normal or only slightly increased $TBNa^+$ (64, 65). A common feature of SIADH is the substantial lack of edema, possibly due to a compensatory release of brain and natriuretic peptides, which balances H_2O retention with a parallel decrease of $TBNa^+$ (66). Urine osmolality is usually >100 mOsm/kg, and most often absolutely normal, similar to urinary Na^+, at balance with the daily intake of 50-150 mEq. This is inappropriate for such low plasma levels of Na^+, whose renal loss should cease, in order to bring back levels to normal. This is usually the case in hypovolemic cases, when the kidney "spares" urine Na^+ through reabsorption, much as in pre-renal forms of acute renal failure (uNa^+<20 mEq/l). Persistently elevated urine Na^+ should prompt differential diagnosis with a Na^+-wasting syndrome, which is usually volume-depleting, with arterial hypotension. This is the case of certain salt-losing nephritides, including pyelonephritis, tubulo-interstitial nephritis, or the juvenile nephronophthysis/medullary cystic disease complex (67).

Differential diagnosis

Occasionally, a saline infusion test is required to differentiate Na^+-depleted patients from SIADH (61). In the 1st group, infusion of 2000 ml isotonic saline over 24 h results in an increase of plasma Na^+, with marginal effects on the fractional excretion of Na^+ (FENa). To the contrary, in SIADH a sharp rise of FENa prevents or even aggravates hyponatremia, with the mechanisms discussed below for the "reset osmostat" syndrome (61).

Clinical features

Renal function and circulating volume are typically normal, with a urine output only slightly reduced (Table 4). True oliguria is rare, while plasma creatinine and urea levels are usually low, not just for dilutional reasons, but also due to the increased FE. Volume expansion may be responsible for decreased urea reabsorption, and the same probably applies to urate reabsorption (see below). Acid-base balance and K^+ excretion are also normal, as a result of H^+ entry into cells compensating HCO_3^- decrease through dilution in an increased TBW. Hypokalemia is counteracted by K^+ efflux from cells. A typical feature of SIADH is hypouricemia, due to increased FE of urates (68-70). It appears that the 2 components of reabsorption, so-called pre-secretory and post-secretory, are both inhibited. This finding is common to other settings of volume expansion, such as pregnancy, parenteral nutrition, or (hypotonic) fluid loading (68-70). It is indeed well known that circulating urate levels are useful indicators of the volume status.
Most patients with "reset osmostat" or SIADH have no obvious neurological abnormalities, provided that the onset of hyponatremia is slow (71). This allows for progressive osmolyte loss from central neurons to occur, thus limiting H_2O entry and therefore intracellular edema, i.e. brain cell swelling. Since Na^+ is very low intracellularly, other osmolytes are extruded from neurons, such as K^+, Cl^-, taurine, inositol, urea, and glutamate (63-65, 71). Nevertheless, thorough neurological testing can identify even minor, unapparent hyporeflexia or decaying cerebral function in subclinical, chronic hyponatremia. Patients with sudden drops of plasma Na^+ may on the con-

Table 4 - *Clinical features of "classic" syndrome of inappropriate ADH secretion.*

Essential diagnostic features
Decreased measured plasma osmolality (<275 mOsm/kg)
Urinary osmolality >100 mOsm/kg during hypotonicity
Euvolemia or hypervolemia
Urinary sodium >30 mmol/l at a standard dietary salt intake
Normal thyroid, adrenal, and renal function
No recent use of diuretic agents
Supporting diagnostic features
Plasma uric acid <4 mg/dl (<0.24 mmol/l)
Blood urea nitrogen <10 mg/dl (<3.6 mmol/l)
Fractional sodium excretion >1%; Fractional urea excretion >55%
Failure to improve hyponatremia after 0.9% saline infusion
Improvement of hyponatremia with fluid restriction

trary experience serious neurological impairment, including confusion, dizziness, lethargy, and rarely progressing to seizures and coma (71-76). To the other extreme, sharp rises of plasma Na^+ during rescue therapy (i.e., >10 mEq/l/day) may bring about further neurological damage, up to the feared iatrogenic complication, pontine myelinolysis (71-76).
In order to differentiate "true" SIADH from the type B, "reset osmostat" syndrome, an accepted approach is to monitor fluid balance upon an oral H_2O load of 10-15 ml/kg BW. A normal individual or a "reset osmostat" subject would usually respond with a watery diuresis leading to the loss of 80% of the administered H_2O over 4 h. On the contrary, SIADH patients would retain most of the H_2O, with a weight gain of about 1 l and actual worsening of hyponatremia.

TREATMENT OF SIADH

Hyponatremia represents a biochemical alteration that deserves careful evaluation by the clinician. Therapeutic strategies should include the removal of the cause, whenever possible, together with the correction of sodium imbalance. In SIADH, the treatment is based on therapeutic algorithms that substantially apply to both euvolemic and hypervolemic hyponatremia, as opposed to the treatment of hypovolemic hyponatremia. Thus, the following sections will report information regarding the management of SIADH and also of conditions of hypervolemic hyponatremia, as it may occur, for instance, in congestive heart failure (CHF), cirrhosis, nephrotic syndrome, and renal failure.

A) The "classical" management

The first aspect to be considered in the management of patients with euvolemic or hypervolemic hyponatremia is represented by the identification and treatment of the underlying causes. In the case of euvolemic hyponatremia, for instance, drugs that may induce SIADH should be withdrawn, if possible, and hormone replacement therapy should be started in patients with suspected hypothyroidism or hypocortisolism, after hormonal evaluation has been performed (77).
The most important factor that influences the treatment strategy aiming to correct sodium imbalance is the presence of neurological manifestations: symptoms are related to the severity and particularly to the rate of the fall in plasma sodium levels (78). Patients with acute (i.e. onset within 48 h) and severe hyponatremia (≤120 mEq/l) are usually symptomatic and they need a close surveillance because of the great risk to develop neurological complications, such as seizures, coma, and brain herniation. In such conditions, hyponatremia should be corrected relatively quickly. Conversely, patients with chronic hyponatremia (onset >48 h) have usually minimal neurological manifestations and it is possible to find long-standing hyponatremic patients who are completely asymptomatic, even in the presence of very low plasma sodium levels. Anyway, considering the negative consequences that even a mild and chronic hyponatremia may determine on health status, the distinction between symptomatic and asymptomatic forms of hyponatremia should be essentially intended as a schematic aid for defining appropriate therapeutic intervention by the clinician. With this in mind, based on the presence or absence of evident symptoms, the management of euvolemic or hypervolemic hyponatremia should proceed as follows.

Asymptomatic hyponatremia

Fluid restriction is considered the first-line approach in asymptomatic patients, with initial fluid intake reduced to 800-1200 ml/24-h (79). Especially in hospitalized patients, the amount of fluid intake in the following days can be established on the basis of 500 ml/day below the average daily urine volume (80). Considering that patients with SIADH have also a negative total body sodium balance, an increase in NaCl intake might be considered if not contraindicated (81). This approach allows a progressive depletion of TBW and a gradual increase in plasma sodium levels. However, it has to be reminded that, in patients with SIADH, thirst is inappropriately normal due to a decrease in the osmotic thirst threshold (82), and therefore in the long-term fluid restriction tends to become uncomfortable for the patient. Because of the difficulty in maintaining fluid restriction, possible pharmacological approaches have been considered.
The use of drugs which reduce the renal action of AVP, yet not approved for the correction of hyponatremia, might be helpful in managing euvolemic or hypervolemic hyponatremia. One of these is demeclocycline, a tetracycline derivative, which causes (with an unknown mechanism of action) nephrogenic DI in about 60% of patients (79). Doses ranging from 600 to 1200 mg/day are necessary to obtain a pharmacological effect, but the use of this drug has been limited due to several problems. First, ADH-resistance is not predictable and a large proportion of patients do not develop nephrogenic DI. Second, the treatment must be continued for several days because the onset of action is delayed and up to 2 weeks may be necessary to restore normal plasma sodium concentrations. Third, demeclocycline has side effects, such as photosensitivity and in particular nephrotoxicity, which limit its use in patients with cirrhosis and CHF (78). Another possible pharmacological approach is represented by lithium that reduces the renal action of ADH by downregulating ADH-stimulated AQP-2 expression (83). About 30% of patients develop nephrogenic DI (84) but, similarly to demeclocycline, the use of lithium is limited by the high prevalence of side effects. In fact, chronic lithium therapy may determine nephrotoxicity [i.e. interstitial nephritis (85) or renal failure (86)] and endocrinological disorders, such as hypothyroidism and hyperparathyroidism (79). Urea has been considered useful in the treatment of SIADH, as well as in the management of hypervolemic hyponatremia (87). It can be administered orally at the dosage of 30 g/day, but its unpleasant taste represents a problem for the patient. It corrects hypo-osmolality by increasing solute-free water excretion and by decreasing urinary sodium excretion (81). The efficacy of urea in the long term has been demonstrated in humans (88); there are also data in rat models, suggesting the possibility that urea may have a protective effect against brain complication related to hyponatremia treatment, such as myelinolisis (89, 90). Nevertheless, be-

cause of poor palatability, gastrointestinal symptoms, and the development of uremia at higher doses, urea is rarely used in the management of hyponatremia. Lastly, phenytoin has been shown to suppress ADH secretion in some cases of SIADH, but responses have been erratic and unpredictable (91).

Symptomatic hyponatremia

In patients with symptomatic euvolemic hyponatremia, infusion of hypertonic saline (3% NaCl) should be considered as the first-line therapy. In these patients, the use of isotonic saline should be avoided because it can worsen hypo-osmolality. Actually, in SIADH only renal water handling is impaired, whereas renal sodium handling is normal. Therefore, in order to avoid a further reduction of sodium plasma levels, the osmolality of the fluid given must exceed the osmolality of the urine (92). Hypertonic saline is usually combined with iv furosemide, in order to limit treatment-induced expansion of the extracellular-fluid volume and to promote net H_2O excretion driven by substantial natriuresis, at balance with the iv Na^+ load. As an example, 1000 ml of 3% saline contain approx. 1026 mEq NaCl or mOsm/kg. If urine osmolality is set by the kidney at 500 mOsm/kg, the net amount of H_2O needed to excrete the NaCl load will be about 2000 ml, with the desired negative H_2O balance. In other words, furosemide-induced diuresis is equivalent to giving a one-half isotonic saline solution, thus favoring the correction of hyponatremia. This is particularly important in hypervolemic patients, in whom loop diuretic administration should anticipate hypertonic saline infusion (81). A crucial point is the rate of correction of hypotonic hyponatremia, due to the possibility that an inappropriate increase in sodium concentrations exposes patients to the risk of developing cellular dehydration and neurological sequelae, possibly leading to the letal central pontine myelinolysis (CPM). According to most reported cases of CPM that have occurred after an increase of natremia >12 mEq/l per day, a rate of correction <10-12 mEq/l in the first 24 h or <18 mEq/l in 48 h has been suggested (93). However, considering that some cases of CPM have also occurred after an increase of 9 mEq/l per day, a rate of correction not exceeding 8 mEq/l appears more appropriate (9). In the evaluation of the risk to cause CPM, it should be also taken into account the presence of predisposing factors, such as severe hyponatremia (<105 mEq/l), chronic alcoholism, liver disease (i.e. hepatitis or cirrhosis), malnutrition, thiazide therapy, and hypokalemia (94). In clinical practice, an initial hourly rate of correction of 0.5-1.0 mEq/l is usually recommended in patients with chronic symptomatic hyponatremia (3). Instead, in patients with acute symptomatic hyponatremia, who are at high risk of cerebral edema, cerebral herniation, and death, serum sodium levels should be initially increased by 1-2 mEq/l per h until life-threatening manifestations disappear (9). During infusion of hypertonic saline the condition of the patient and sodium levels must be carefully monitored (at least every 4 h, better if every 2 h) and the infusion should be stopped when the patient becomes asymptomatic and/or safe sodium levels (≥120 mEq/l) are reached and/or the total magnitude of correction achieved 18 mEq/l (81). A formula to calculate the rate of saline infusion is shown in Table 5.

Table 5 - *Formula for the calculation of the infusion rate of saline solution.*

$$[1]\text{Change in serum } Na^+ = \frac{[2]\text{infusate } Na^+ - [3]\text{serum } Na^+}{[4]\text{total body water} + 1}$$

[1]change in serum Na^+ after 1 l of any infusate

[2]infusate Na^+ = 513 mmol/l if hypertonic saline (3% NaCl)
154 mmo/l if isotonic saline (0.9% NaCl)

[3]serum sodium = serum sodium concentration of the patient

[4]total body water is calculated as a fraction of body weight (the fraction is 0.6 and 0.5 in non-elderly men and women, respectively; 0.5 and 0.45 in elderly men and women, respectively)

B) The new frontier in the therapeutic algorithm of euvolemic and hypervolemic hyponatremia: The vaptans

Mechanism of action and clinical trials

V_2 non-peptide receptor antagonists, known as vaptans, represent a new and very promising alternative approach for the treatment of euvolemic and hypervolemic hyponatremia. They have been termed aquaretics to distinguish them from diuretics, because they promote solute-free water excretion by the kidney. By counteracting the binding of ADH to V_2 receptors, vaptans block the activation of the intracellular signaling pathway, which leads to the translocation of AQP-2 from cytoplasmic vesicles to the plasma membrane, a rate-limiting step for the transepithelial movement of water. A schematic representation of the mechanism of action of vaptans is shown in Figure 1. About 3% of AQP-2 present in collecting duct cells is excreted into urine. Thus, the aquaretic effect of vaptans can be determined by measuring AQP-2 excretion (95). This new class of drugs includes selective V_2-receptor antagonists, such as, for instance, tolvaptan, lixivaptan, and satavaptan, and a V_{1a}/V_2-receptor antagonist, i.e. conivaptan. Because of its concomitant V_{1a} receptor antagonism, conivaptan has been considered particularly suitable for patients with CHF, who may benefit from the increased cardiac output and reduced vascular resistance induced by V_{1a} receptor blockade, which causes vasodilation of vascular smooth muscle. V_{1a} receptor antagonism may also prevent ADH-induced coronary artery vasoconstriction and a direct myocardial remodeling stimulus (96). The efficacy and safety of conivaptan were, for instance, assessed in a randomized, placebo-controlled short-term trial in patients with symptomatic CHF (class III-IV NYHA) (97). Patients received a single iv dose of conivaptan (10-20-40 mg) or placebo. Compared to placebo, 20 and 40 mg conivaptan significantly reduced pulmonary capillary wedge pressure and right atrial pressure over the 12-h period following treatment, and increased urine output. In another study, oral conivaptan (40 or 80 mg/day) or placebo was administered for 5 days in 74 patients with euvolemic or hypervolemic hyponatremia (baseline serum sodium levels ranging from 115 to 129 mEq/l) (98). Conivaptan determined a significantly higher mean change in serum sodium than placebo and the median time to achieve an increase of ≥4 mEq/l from baseline was lower. Normal serum sodium levels were obtained in 71% and in 82% of patients given conivaptan (40 and 80 mg/day, respectively), and in 42% of patients

given placebo. The drug was well tolerated. In December 2005 the U.S. Food and Drug Administration (FDA) approved the intravenous form of conivaptan for short-term treatment of euvolemic or hypervolemic hyponatremia in hospitalized patients.

Lixivaptan is a selective oral V_2-receptor antagonist. The effectiveness of this drug has been assessed in studies, which involved patients with SIADH, liver cirrhosis, and CHF. For instance, in a phase II small trial including 6 patients with SIADH, who received lixivaptan (50 or 100 mg twice daily) or placebo, the increase of serum sodium induced by lixivaptan was significantly higher than the effect of placebo at 72 h (99). Two multicenter, randomized, double blind, placebo-controlled phase III clinical trials aiming to assess the effectiveness, safety, and tolerability or lixivaptan capsules specifically in patients with euvolemic hyponatremia are currently ongoing (www.clinicaltrials.org, NCT00660959 and NCT00876798). With regard to liver cirrhosis, in a phase II multicenter trial, 60 hospitalized patients affected by this condition, with ascites and hyponatremia, were randomized to placebo or lixivaptan (100 or 200 mg/day). The primary end-point, i.e. sodium normalization within 7 days of treatment, was achieved by 27% and 50% of patients receiving 100 or 200 mg lixivaptan, respectively, whereas sodium normalization was not obtained in any patient receiving placebo (100). Studies in patients with CHF have shown that lixivaptan may be a potential therapeutic for the associated dilutional hyponatremia that occurs in these patients. For instance, a double-blind, randomized study conducted in 42 patients with NYHA class II-III CHF showed that lixivaptan effectively increased urine volume, solute-free water excretion, and serum sodium (101). A phase III study, Treatment of Hyponatremia Based on Lixivaptan (BALANCE), is now underway. The study will be a multicenter, randomized, double-blind trial on the use of lixivaptan with a primary end-point of change in serum sodium from baseline values after 1 week of treatment. Results of this trial should provide more data on effectiveness and safety of this drug in CHF patients (102).

Satavaptan, also orally active, has been successfully tested for instance in a phase III study, in which 34 patients with SIADH received 25 or 50 mg once a day for 5 to 23 days, or placebo in a double-blind, randomized fashion (103). The rate of responders (i.e. patients who achieved serum sodium normalization or an increase of at least 5 mEq/l from baseline) was significantly higher in patients receiving satavaptan (both 25 or 50 mg/day). The study was then extended up to 12 months in an open-label trial, in order to assess long-term efficacy and safety of satavaptan. Serum sodium response was maintained with a good safety profile. In a multicenter, double-blind, randomized, controlled study, sativaptan (5, 12.5, or 25 mg once a day) was administered to patients with cirrhosis, ascites, and hyponatremia (104). At the end of the treatment period (14 days), all doses of sativaptan determined a better control of ascites than placebo, together with an effective increase of serum sodium. Thirst was more common in patients treated with satavaptan, whereas other adverse events were similar among groups.

Tolvaptan, the first oral vaptan approved for the treatment of SIADH

Tolvaptan is a selective oral V_2-receptor antagonist, which has been shown to be more effective than fluid restriction in correcting euvolemic or hypervolemic hyponatremia (105). Moreover, tolvaptan determines a

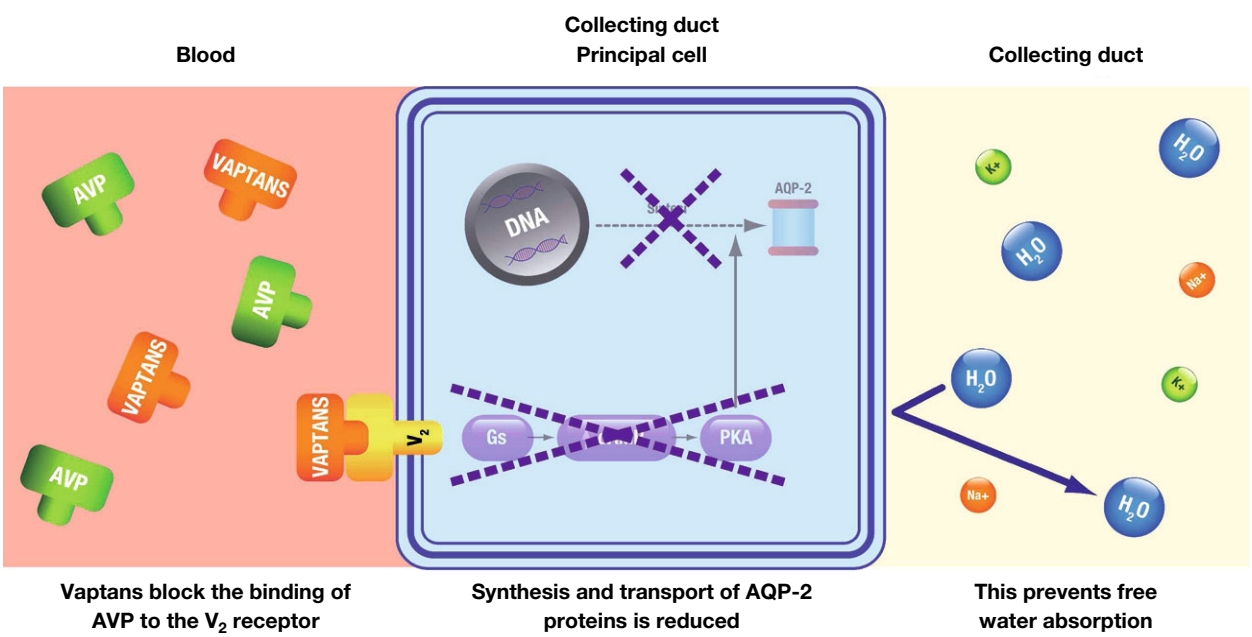

Fig. 1 - *Schematic representation of the mechanism of action of vaptans.*

greater aquaresis than furosemide and hydrochlorothiazide without interfering in sodium and potassium renal tubular excretion (106). The role of tolvaptan in patients with mild to moderate (130-134 mEq/l and 121-129 mEq/l, respectively) euvolemic and hypervolemic hyponatremia has been evaluated in two multicenter, randomized, double-blind, placebo-controlled phase III trials [Study of Ascending Levels of Tolvaptan in hyponatremia -1 and -2 (SALT-1 and SALT-2)] (107). Patients were randomly assigned to placebo (no.= 223) or tolvaptan (no.= 225). The dose was titrated from 15 to 60 mg/day on the basis of serum sodium concentration. The two primary end-points of the two studies were the change in the average daily area under the curve for serum sodium concentration from baseline to day 4 and from baseline to day 30 of treatment. In both SALT-1 and SALT-2 serum sodium increase was higher in patients treated with tolvaptan both after 4 days and after 30 days of therapy. Within a week after discontinuation of tolvaptan administration, hyponatremia recurred. In only 4 of the 223 patients receiving tolvaptan the rate of correction in the first 24 h exceeded 0.5 mEq/l/h and in 4 cases sodium levels rose above 146 mEq/l. Tolvaptan was well tolerated and the most frequent side effects were thirst, dry mouth, and increased diuresis, which were in agreement with the mechanism of action of the drug. Another randomized, double-blind, placebo-controlled, event-driven phase III trial [Efficacy of Vasopressin Antagonism in Heart Failure: Outcome Study with Tolvaptan (EVEREST)], comprised 4133 patients, who were hospitalized with heart failure in North and South American and in European centers (108). The minimum treatment time was 60 days and the 2 primary end-points were all-cause mortality and cardiovascular death or hospitalization for CHF, whereas secondary end-points included changes in edema, dyspnea, and body weight. During a median follow-up of almost 10 months there was no significant difference between patients receiving oral tolvaptan (30 mg/day) or placebo with regard to the primary end-points. However, shortly after the initiation of treatment, tolvaptan significantly improved edema and dyspnea and reduced body weight. Furthermore, in patients with hyponatremia, serum sodium levels significantly increased. The safety and effectiveness of tolvaptan in chronic hyponatremia was further evaluated in a multicenter, open-labeled extension of SALT-1 and -2 (SALTWATER) (109). A total of 111 patients received oral tolvaptan for a mean period

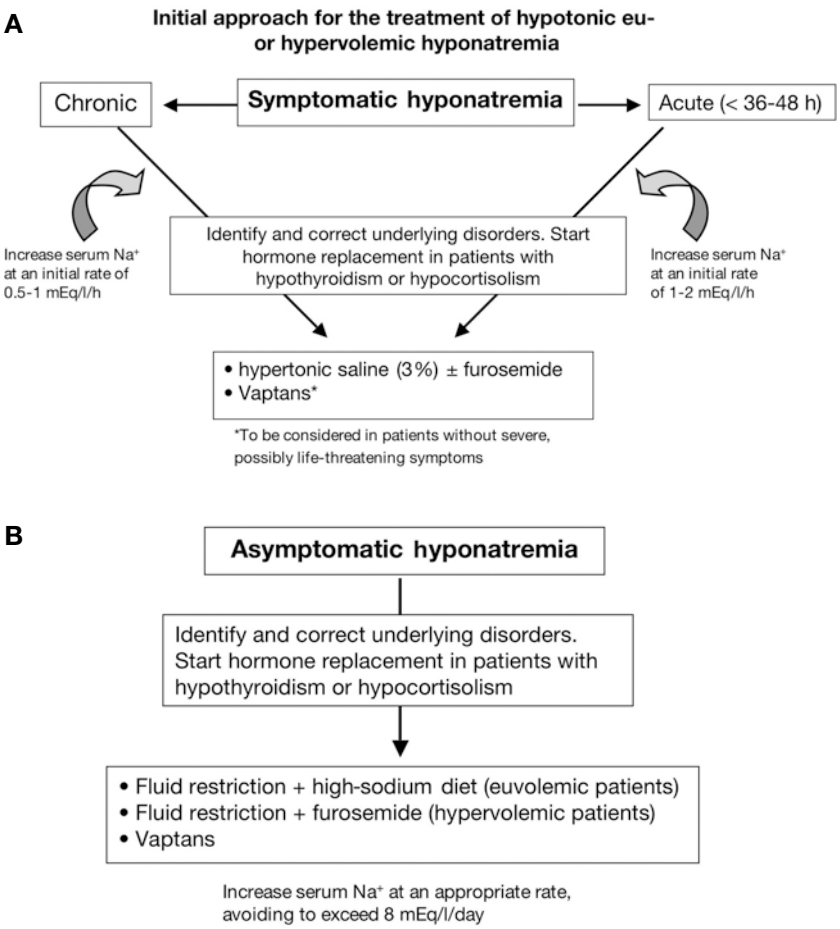

Fig. 2 - *Schematic representation of the therapeutic algorithm in patients with symptomatic (A) or asymptomatic (B), hypotonic, euvolemic or hypervolemic hyponatremia.*

of 701 days. Mean serum sodium levels increased from 130 mEq/l at baseline to >135 mEq/l throughout follow-up. The most frequent adverse events were superimposable with those observed in the SALT-1 and -2 trials; 6 drug-related adverse effects led to the discontinuation of treatment, whereas in 5 patients the increase in serum sodium exceeded the desired 1 mEq/l/h at the beginning of treatment. In conclusion, the SALTWATER study provided evidence that prolonged administration of tolvaptan maintains effectiveness in controlling serum sodium and has a satisfactory safety profile. In May 2009 tolvaptan was approved by FDA to treat hyponatremia associated with CHF, liver cirrhosis, and SIADH. Shortly after (August 2009) the European Commission approved tolvaptan as the first oral vaptan for the treatment of hyponatremia secondary to SIADH. Due to the need for a dose titration phase with close monitoring of serum sodium and volume status, treatment should be initiated in hospitalized patients.

Vaptans: Final considerations and perspectives

The effectiveness and safety of V_2-receptor antagonists has been highlighted by a very recent review and meta-analysis, which identified 15 randomized controlled trials (RCT) (110). The meta-analysis revealed that V_2-receptor antagonist treatment significantly increased the rate of serum sodium normalization compared to placebo or no treatment in euvolemic and hypervolemic patients, with a greater effect in the former group. Change from baseline serum sodium was significantly increased in patients receiving a vaptan. Finally, although this class of drugs determined an increased rate of rapid sodium correction, hypernatremia rates were not significantly higher compared to placebo or no treatment, adverse events were not increased and no case of CPM was reported. Therefore, vaptans may be considered a new effective tool, and the first available specific drugs, for the treatment of euvolemic and hypervolemic hyponatremia and may find a proper space particularly in asymptomatic or mildly symptomatic (i.e. mild neurocognitive symptoms, depression). This new treatment modality appears very appealing, if we consider also that fluid restriction has a slow onset of action (2-3 days) and may not be easily tolerated or performed by patients, especially if it has to be continued for a prolonged time, as already mentioned. Vaptans might also be effective in patients with moderate hyponatremia-related symptoms (i.e. nausea, confusion, disorientation, unsteady gait), whereas in patients presenting severe symptoms (i.e. seizures, coma, respiratory distress) active therapy with hypertonic saline should be started. Patients receiving vaptans should be closely monitored and sodium should be assessed every few hours in the first days of treatment and regularly afterwards. This is particularly important, if we take into account that the effect of the drug may change during chronic therapy, due for instance to a fluctuating ADH secretion (i.e. in paraneoplastic SIADH) or to the presence of interfering drugs. With regard to this point, it is worth mentioning that vaptans are substrates and also inhibitors of the cytochrome P450 isozyme CYP3A4. Therefore, their concentration may be increased by the concomitant use of strong CYP3A4 inhibitors (i.e. anti-fungal drugs, such as ketoconazole and itraconazole, anti-viral drugs such as ritonavir and indinavir, macrolides) and, on the contrary, may be decreased by CYP3A4 activators, such as barbiturates, phenytoin, and carbamazepine. For this reason, the use of V_2-receptor antagonists together with strong inhibitors or activators of CYP3A4 should be in principle avoided. In case a V_2-receptor antagonist is used together with an activator of CYP3A4, an increase of the dose should be taken into account. A schematic representation of a proposed therapeutic algorithm for the treatment of hypotonic euvolemic or hypervolemic hyponatremia is shown in Figure 2.

CONCLUSIONS

Hyponatremia is a rather common electrolyte disorder in hospitalized patients and it is a sign that should be always considered with great attention by the clinician. There is a high prevalence of chronic hyponatremia in the elderly, frequently due to SIADH (or SIAD, as it has been also called more recently). There is increasing awareness that even mild and asymptomatic forms of hyponatremia may determine clinically relevant consequences. With regard to this point, one of the most surprising and worth mentioning findings is the very recent demonstration by the group of J. Verbalis that chronic hyponatremia causes a significant decrease of mineral density and is associated with increased odds of osteoporosis (111). In such a scenario, the opinion of the authors of this review is that V_2-receptor antagonists, if correctly managed, will have a profound clinical impact in the years to come, because of their demonstrated efficacy and safety profile in the treatment of euvolemic and hypervolemic forms of hyponatremia.

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