Management of Severe Hyponatremia and SIADH

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Case Presentation

A 51 year old woman with hypothyroidism, diabetes and hypertension presented with two weeks of progressive fatigue, weakness, and difficulty walking. In the emergency department she complained of lightheadedness and dizziness. Her initial blood pressure was 70/42. She was awake and alert, with 4/5 strength throughout. Her son had recently passed away and she reported decreased appetite, decreased oral intake, and weight loss. She had been smoking one pack of cigarettes per day since age 11. Initial serum sodium was 117 mmol/L, urine sodium 69 mmol/L, and urine osmolality 576 mOsm/kg. She was treated with 2 liters (L) of intravenous (IV) 0.9 % saline, and blood pressure improved to her baseline, 117/74.

Question What is the cause of this patient's severe hyponatremia, and with what urgency should it be corrected?

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Answer Evaluate volume status and sodium balance, and correct slowly.

Most patients with severe hyponatremia do not need urgent correction. Time should be taken to evaluate for underlying cause, treating slowly and monitoring sodium levels frequently. This patient was admitted with symptoms attributable to hyponatremia but no critical neurologic findings, so rapid sodium correction was not necessary. Initial IV fluids corrected blood pressure. At that point, the patient was euvolemic and still hyponatremic at 119 mmol/L. Urine sodium and osmolality were consistent with the syndrome of inappropriate antidiuretic hormone activity (SIADH), though measured serum osmolality results were not available. With SIADH the most likely diagnosis, fluids were restricted to 1 L per day and oral sodium chloride (NaCl) tablets begun. Serum sodium increased to 121 mmol/L by day 4 and the patient was transferred to the medical wards. Thereafter, she was found to be orthostatic and treated with IV normal saline. Serum sodium initially remained stable on IV fluids, and repeat studies demonstrated urine sodium 140 mmol/L, urine osmolality 389 mOsm/kg, and serum osmolality 256 mOsm/kg, consistent with SIADH. By hospital day 10, despite resuming fluid restriction and escalating oral NaCl doses, serum sodium had decreased to 113 mmol/L, and the patient remained neurologically intact. Tolvaptan was begun and serum sodium increased to 120 mmol/L within 24 h, remaining stable in the mid-120s. Chest imaging

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demonstrated a 2.5 cm left upper lobe nodule concerning for malignancy which proved to be the cause of her SIADH.

Principles of Management

Risk Stratification

Severely depressed mental status or seizures in acute onset hyponatremia (<48 h) suggest cerebral edema and mandate intensive care unit (ICU) admission and urgent correction of serum sodium concentration. All patients with acute onset severe hyponatremia (serum sodium concentration <120 meq/L), even those without symptoms, are at risk for cerebral edema and should receive urgent serum sodium correction in the ICU [1]. In most cases, asymptomatic patients with severe chronic hyponatremia benefit from ICU admission for monitoring of symptoms and rate of correction during initial management.

Evaluation

In patients not requiring emergent correction, the first step is clinical determination of volume status using history and physical exam. Physical exam findings for volume status are listed in Table 46.1. Table 46.2 presents common hyponatremia syndromes in the ICU by volume status. Serum osmolality less than 275 mOsm/kg water and urine osmolality greater than 100 in a hyponatremic patient with normal salt intake suggests renal free water retention which may be considered "inappropriate" if the patient is euvolemic. Spot urine sodium ≥40 mmol/L is further evidence of free water retention [2]. Once SIADH is diagnosed workup should begin for underlying cause. The most common causes of SIADH in the ICU are summarized in Table 46.3. Evidence of antidiuretic hormone (ADH) activity in a hypovolemic or hemodynamically unstable patient should be expected as a compensatory mechanism and *not* taken to represent SIADH. In cases of indeterminate volume status, it is acceptable to infuse 500 mL to one liter of 0.9 % sodium chloride. Improvement in serum sodium suggests an element of hypovolemia, whereas further reduction in serum sodium with increased urine sodium and urinary osmolality ≥100 suggest SIADH [3]. The discrimination between SIADH and cerebral salt wasting (CSW) is difficult. CSW occurs after brain injury or neurosurgical procedures. Urinary salt and chloride losses cause diuresis and hypovolemia which drives ADH secretion and free water retention. Diagnosis requires proof that urinary sodium losses and volume depletion preceded the development of hyponatremia [1].

Table 46.1 Physical exam findings for volume status

Hypovolemic	Euvolemic	Hypervolemic
Orthostasis Poor skin turgor Dry mucous membranes	Normal heart rate and blood pressure Normal skin turgor Moist mucus membranes	Lower extremity or sacral edema Ascites

Correcting Serum Sodium

If hypovolemia is present or suspected, 0.9 % saline infusion should be administered. For patients with severe acute or symptomatic hyponatremia, hypertonic (3 %) saline should be infused at a rate of 1–2 ml/kg actual body weight [2]. Correction of serum sodium concentration by 4–6 meq/L in the first 2–3 h is sufficient to significantly reduce intracranial pressure and increase cerebral perfusion pressure [4]. Serum sodium should be monitored hourly and infusion stopped when symptoms resolve. For patients who do not require emergent rapid correction of serum sodium concentration, management should be tailored to the underlying condition. Management of the hypervolemic hyponatremias requires addressing underlying organ dysfunction (Table 46.2). Glucocorticoid or thyroid hormone deficiency, discussed elsewhere, can be treated by supplementing these hormones. Severe hyponatremia from CSW may initially require hypertonic saline, though in most cases volume expansion

Table 46.2 Common causes of hyponatremia in the ICU, by volume status

Hypovolemic	Euvolemic	Hypervolemic
Cerebral salt wasting Excessive diuretic therapy GI fluid losses Hemorrhage Burn Adrenal insufficiency Hyperglycemia	SIADH Large volume hypotonic fluid infusion during surgery Primary polydipsia Endurance exercise Ecstasy use Hypothyroidism Adrenal insufficiency Low solute diet	Congestive heart failure Cirrhosis Nephrotic syndrome Renal failure

Table 46.3 Common causes of SIADH in the ICU

ICU care-associated	Malignant	Pulmonary	Neurologic	Pharmacologic
Anesthesia Pain Positive pressure ventilation Nausea	Small cell lung cancer Head and neck cancer Prostate cancer Lymphoma Brain tumor	Cystic fibrosis Pneumonia	Head trauma Intracranial hemorrhage CNS infection Stroke Guillain Barré Delirium Tremens	Narcotics Methylenedioxy-N-methamphetamine (Ecstasy) Nicotine Antipsychotics NSAIDs Vasopressin Cyclophosphamide

with isotonic saline is sufficient [2]. SIADH is managed with fluid restriction and ensuring adequate dietary sodium and protein intake. In the ICU, total fluid intake should be limited to 500 mL less than daily urinary output, and should account for oral fluids, solid foods, and IV medications [5].

Monitoring Correction Rate

In patients with asymptomatic chronic hyponatremia, there is virtually no risk of death from cerebral edema. Accordingly, guidelines and expert opinion recommend that correction be limited to 6–8 meq/L per day, with serum sodium checks every 2–4 h. During correction of hypovolemic hyponatremia, urinary output must be monitored closely, for which a urinary catheter is helpful. Once the hypovolemic stimulus for ADH secretion has been relieved, ADH levels will drop, urinary output will increase, and serum sodium concentration will increase rapidly. At this point the isotonic saline solution should be stopped and serum sodium monitored carefully. If correction proceeds at a rate greater than 0.5 meq/L/h for more than 4 h, rate of rise can be slowed by administering hypotonic fluids or IV desmopressin 2–4 micrograms [5].

Osmotic Demyelination Syndrome (ODS)

In the setting of serum hyponatremia, brain cells extrude organic solutes, which prevents cerebral swelling. This process takes about 2 days, but when hyponatremia is corrected, it can take up to a week for cells to recapture lost osmolytes. If serum sodium correction outpaces solute recapture, central pontine or extrapontine myelinolysis results. ODS classically has a biphasic presentation: the patient's neurologic status initially improves with serum sodium correction, but days later, pseudobulbar palsy and quadriparesis develop. Most described cases of ODS resulted from serum sodium correction greater than 10–12 mmol/L in 24 h or 18 mmol/L in 48 h, though slower rates of correction have been associated with this syndrome in high-risk patients including those with alcoholism, cirrhosis and severe malnutrition [5].

Evidence Contour

Diagnostics

Spot urine sodium concentration is used to support a diagnosis of SIADH but is less useful in patients on diuretics due to natriuretic effect. One study demonstrated that for patients on diuretics, **the fractional excretion of uric acid** performed just as well as urine sodium concentration in patients not on diuretics, with values over 12 % consistent with SIADH [6].

Spot urine sodium concentration is a fairly good stand-alone test for SIADH, with one study demonstrating a diagnostic accuracy of 0.82 for urine sodium 50 meq/L or greater [7].

Novel Treatments

Vasopressor receptor antagonists (**vaptans**) bind the vasopressin type 2 (V_2) receptor in the distal nephron to cause excretion of free water. Four large studies of vaptans (conivaptan and tolvaptan) in patients with euvolemic or hypervolemic hyponatremia demonstrated significant short-term and lasting improvement in serum sodium concentration. In the SALT-1 and SALT-2 trials, average sodium levels increased from 129 to approximately 135 at days 4 and days 30. Adverse events included dehydration, renal dysfunction, hypernatremia, and overly rapid serum sodium correction [8–10]. Concerns regarding safety of vaptans in the ICU center on their ability to cause significant aquaresis and hypovolemia and the potential for overly rapid correction of serum sodium. Hyponatremia in ICU patients is often multifactorial, and patients with SIADH may have concomitant intravascular hypovolemia. For this reason, many experts recommend withholding vaptans even for strongly suspected SIADH until euvolemia is certain [5].

Urea has been described as a treatment for SIADH. It causes renal sodium retention and free water excretion but tastes very bad [11]. Excellent results have been reported for the administration of urea via enteric tubes along with moderate amounts of isotonic saline in ICU patients with hyponatremia [11–13].

Osmotic Demyelination Syndrome

Outcomes

Outcomes for ODS have historically been presumed to be very poor, but in a 2012 study of 36 patients with ODS, 14 patients survived without significant disability at one year. Patients with alcoholism were more likely to have poor outcomes [14].

Prevention

In animal models of chronic hyponatremia, **rapid relowering of the serum sodium concentration** after excessive correction can prevent ODS [15]. Two case reports have demonstrated success of this approach in patients who developed neurological symptoms after overly rapid correction [16, 17].

Patients with chronic renal failure rarely develop ODS despite large and rapid corrections of hyponatremia with hemodialysis [18, 19]. Induced renal failure and exogenous **urea** administration increase the rate of brain osmolyte reaccumulation and prevent ODS during rapid sodium correction in rats; no human studies of urea for ODS prevention exist [20, 21].

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