The Syndrome of Inappropriate Antidiuresis

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A 62-year-old woman noted an unpleasant, sweet taste in her mouth. She otherwise felt well and was taking no medications. Because dysgeusia is a rare manifestation of hyponatremia, her serum sodium level was tested and was 122 mmol per liter. The serum osmolality was 250 mOsm per kilogram of water, the urinary osmolality 635 mOsm per kilogram of water, the urinary sodium 85 mmol per liter, and the urinary potassium 40 mmol per liter. Her thyroid function and adrenal function were normal. A computed tomographic (CT) scan of the thorax showed a mass in the lower lobe of the left lung, which proved to be a small-cell carcinoma. How should her hyponatremia be treated?

The Clinical Problem

Hyponatremia, defined as an excess of water in relation to the sodium in the extracellular fluid, is the most common electrolyte disorder in hospitalized patients. Mild hyponatremia (serum sodium, <135 mmol per liter) occurs in 15 to 22% of these patients and in approximately 7% of ambulatory patients; moderate hyponatremia (serum sodium, <130 mmol per liter) occurs in 1 to 7% of hospitalized patients. Hyponatremia is important to recognize both because of potential morbidity and because it can be a marker of underlying disease.

The syndrome of inappropriate secretion of antidiuretic hormone (SIADH) is the most frequent cause of hyponatremia, although hyponatremia associated with volume depletion of the extracellular fluid also occurs commonly. SIADH was first described in patients with bronchogenic carcinoma in whom a physiologic stimulus for the release of the antidiuretic hormone was lacking. Thus, the level of secretion of the antidiuretic hormone was deemed “inappropriate.” After the syndrome was described, the antidiuretic hormone in humans was found to be arginine vasopressin.

Initial reports suggested that secretion of arginine vasopressin in SIADH was independent of plasma osmolality. Although this is the case in about one third of patients with SIADH (Fig. 1), in other patients with this condition, secretion of arginine vasopressin is fully suppressed, resulting in dilute urine, but at a serum sodium level lower than normal (a “reset osmostat”). Less commonly, plasma levels of arginine vasopressin are low or undetectable in patients with SIADH, even in the presence of hyponatremia. In some patients, mutations of the aquaretic (i.e., water-channel–regulating) vasopressin receptor are present, resulting in concentrated urine in the absence of arginine vasopressin. Because not all patients with the syndrome have elevated circulating levels of arginine vasopressin, the term syndrome of inappropriate antidiuresis (SIAD) was proposed as an accurate description of this condition. Although inappropriate antidiuresis is an essential feature of this syndrome, excessive water intake, driven by nonosmotic stimuli, is also required for hyponatremia to develop.

Certain populations are at increased risk for hyponatremia associated with SIAD.
The risk rises with increasing age and is especially high among residents of nursing homes. Although the causes of SIAD are myriad, they can be categorized as related to malignant diseases, pulmonary diseases, and disorders of the central nervous system, among others (Table 1). In addition, a variety of drugs can stimulate the release of arginine vasopressin or potentiate its action (Table 1); traditionally, some medical authorities include such drugs among the causes of SIAD, whereas others do not include them in this category.

Severe hyponatremia (serum sodium <125 mmol per liter), especially when the condition develops rapidly (within 48 hours), has serious sequelae, including confusion, hallucinations, seizures, coma, decerebrate posture, and respiratory arrest, leading to death. Milder symptoms of hyponatremia include headache, difficulty concentrating, impaired memory, muscle cramps, and weakness; dysgeusia has also been reported. Patients with chronic hyponatremia may be asymptomatic, although some data suggest that neurologic deficits, such as those causing falls, may be more common in patients with chronic hyponatremia than in persons with normal serum sodium levels. The threshold serum sodium levels at which neurologic complications occur appear to be higher among women than among men.

### STRATEGIES AND EVIDENCE

#### DIAGNOSIS

Formal criteria for the diagnosis of SIAD are summarized in Table 2. Serum osmolality must be measured to rule out pseudohyponatremia, a laboratory artifact occurring when levels of serum lipids or proteins are elevated and serum sodium levels are measured by means of common, indirect techniques. Hypertonic (or translocational) hyponatremia occurs when osmotically active solutes (glucose or mannitol) draw water from cells. For each increase of 100 mg per deciliter (5.6 mmol per liter) in plasma glucose levels, serum sodium declines by 1.6 to 2.4 mmol per liter. (The traditional correction factor of 1.6 mmol per liter may underestimate the actual change.) A normal or elevated measured osmolality value, however, does not rule out hypotonic hyponatremia, because urea is an ineffective osmole. Thus, the effective osmolality (sometimes called toxicity) is equal to the measured osmolality minus (blood urea nitrogen + 2.8), with blood urea nitrogen measured in milligrams per deciliter. For a diagnosis of hypotonic hyponatremia, the effective osmolality must be less than 275 mOsm per kilogram of water (Table 2).

To make the diagnosis of SIAD, the urinary osmolality must exceed 100 mOsm per kilogram of water when the effective plasma osmolality is low (Table 2). The presence of clinical euvoolemia is considered to be essential, because depletion of the effective arterial blood volume stimulates the secretion of arginine vasopressin appropriately. When expansion of the volume of extracellular fluid is associated with depletion of the effective arterial blood volume (as in cirrhosis), edema is usually evident. Detecting extracellular-fluid volume depletion as a cause of hyponatremia, however, is more difficult than detecting volume expansion, because the sensitivity of clinical assessment is limited; laboratory tests are often used to provide additional guidance. Hypouricemia, low blood urea nitrogen, and a urinary sodium level greater than 40 mmol per liter in patients...
with hyponatremia suggest SIAD, but are not diagnostic; for example, a serum uric acid level of less than 4 mg per deciliter (238 μmol per liter) (in the presence of hyponatremia) has a positive predictive value for SIAD of 73 to 100%. A urinary sodium level of less than 30 mmol per liter has a positive predictive value of 71 to 100% for an infusion of 0.9% saline to increase the serum sodium level.

When diagnostic uncertainty remains, volume contraction of the extracellular fluid can be ruled out by infusing 2 liters of 0.9% saline over a period of 24 to 48 hours. Even though 0.9% saline is not the preferred treatment for SIAD, it is usually safe when the baseline urinary osmolality is less than 500 mOsm per kilogram of water; correction of the hyponatremia suggests underlying volume depletion of extracellular fluid. Measurement of the serum level of arginine vasopressin is not recommended routinely, because urinary osmolality above 100 mOsm per kilogram of water is usually sufficient to indicate excess of circulating arginine vasopressin.

**Management**

The only definitive treatment of SIAD is elimination of its underlying cause. Most cases caused by malignant disease resolve with effective antineoplastic therapy, and most of those due to medication resolve promptly when the offending agent is discontinued. When the hyponatremia is chronic and asymptomatic, a diagnosis can be pursued before treatment is initiated.

**Acute Symptomatic Hyponatremia**

The most important factors dictating the management of SIAD are the severity of the hyponatremia, its duration, and the presence or absence of symptoms (Fig. 2). For symptomatic patients with severe hyponatremia known to have developed within 48 hours, clinical experience suggests that rapid treatment is warranted. The goal is to raise the serum sodium level by 1 to 2 mmol per liter per hour by infusing 3% saline; these recommended rates are guided by data from case series, in the absence of data from randomized trials, but they are widely accepted. Many authorities recommend concomitant furosemide, although some recommend avoiding it or reserving it for patients with extracellular-fluid volume expansion. Many experts believe that the magnitude of correction during the first 24 hours of treatment should be no
more than 8 to 10 mmol per liter, and during the first 48 hours no more than 18 to 25 mmol per liter, even when the hyponatremia is acute.\textsuperscript{1,6,27} One approach is to aim for the cessation of neurologic symptoms, such as seizures, and then reduce the correction rate.\textsuperscript{25} An increase in serum sodium levels of less than 10 mmol per liter is usually sufficient to reduce the symptoms and prevent complications.\textsuperscript{28} (Specific treatment regimens are discussed below.)

**Hyponatremia of Long or Unclear Duration**

Most cases of hyponatremia that occur out of the hospital are chronic and minimally symptomatic, except in marathon runners, users of 3,4-methylenedioxymethamphetamine (MDMA, also known as “ecstasy”), and people who drink water to excess; in these groups, severe symptoms usually indicate acute hyponatremia and require rapid correction.

The treatment of hyponatremia with an unclear duration and nonspecific symptoms or signs (e.g., headache or lethargy) is particularly challenging. Some reports suggest a high risk if patients are not treated aggressively\textsuperscript{29}; others suggest that rapid correction increases morbidity or mortality.\textsuperscript{30} Unlike patients with acute hyponatremia, those with hyponatremia of longer duration have a documented risk of osmotic demyelination if the serum sodium level is corrected by more than 12 mmol per liter over a period of 24 hours. This disorder, which includes both central pontine and extrapontine myelinolysis, begins with lethargy and affective changes (generally after initial improvement of neurologic symptoms with treatment), followed by mutism or dysarthria, spastic quadriparesis, and pseudobulbar palsy.\textsuperscript{31} Case series and experimental data indicate that this complication may result from rapid correction of hyponatremia that has been present for more than 48 hours.\textsuperscript{31}

To balance the risks of chronic hyponatremia against the risks of rapid correction, many authorities recommend a modest rate of correction (an increase in serum sodium of 0.5 to 1.0 mmol per liter per hour), using lower rates of saline infusion for patients with symptomatic hyponatremia of unknown duration. Many limit correction to 8 mmol per liter over a period of 24 hours and 18 mmol per liter over a period of 48 hours; close monitoring of the rate of correction (every 2 to 3 hours)\textsuperscript{25} is recommended to avoid overcorrection. Some authorities recommend brain imaging (e.g., CT or magnetic resonance imaging) to determine whether cerebral edema is present and to gauge the urgency of the need for correction, although evidence that imaging improves outcomes is lacking.\textsuperscript{32}

Asymptomatic patients with chronic hyponatremia have a low risk of serious neurologic sequelae but a well-described risk of osmotic demyelination with rapid correction.\textsuperscript{31} Therefore, treatment is aimed at correcting the hyponatremia very gradually. Fluid restriction, estimated on the basis of levels of urinary and plasma electrolytes (Fig. 2), is a cornerstone of therapy.\textsuperscript{5,33} The maximum tolerated fluid intake is proportional to the oral osmotic load, so adequate intake of dietary protein and salt should be encouraged. Oral intake of urea (30 g per day) is effective but is poorly tolerated. Demeclocycline (Declomycin, Wyeth–Ayerst) (300 to 600 mg twice daily) reduces urinary osmolality and increases serum sodium levels, but its effects

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**Table 2.** Diagnosis of SIAD.\textsuperscript{9}

| Essential features |  
|--------------------|---|
| Decreased effective osmolality (<275 mOsm/kg of water) |  
| Urinary osmolality >100 mOsm/kg of water during hypotonicity |  
| Clinical euvolemia |  
| No clinical signs of volume depletion of extracellular fluid |  
| No orthostasis, tachycardia, decreased skin turgor, or dry mucous membranes |  
| No clinical signs of excessive volume of extracellular fluid |  
| No edema or ascites |  
| Urinary sodium >40 mmol/liter with normal dietary salt intake |  
| Normal thyroid and adrenal function |  
| No recent use of diuretic agents |  

| Supplemental features |  
|----------------------|---|
| Plasma uric acid <4 mg/dl |  
| Blood urea nitrogen <10 mg/dl |  
| Fractional sodium excretion >1%; fractional urea excretion >55% |  
| Failure to correct hyponatremia after 0.9% saline infusion |  
| Correction of hyponatremia through fluid restriction |  
| Abnormal result on test of water load (<80% excretion of 20 ml of water per kilogram of body weight over a period of 4 hours), or inadequate urinary dilution (<100 mOsm/kg of water) |  
| Elevated plasma AVP levels, despite the presence of hypotonicity and clinical euvolemia |  

\* AVP denotes arginine vasopressin. Data are adapted from Schwartz et al.\textsuperscript{6} and Janicic and Verbalis.\textsuperscript{9} The test for water load and measurement of AVP are rarely recommended. To convert the value for blood urea nitrogen to millimoles per liter, multiply by 0.357.
can be variable and it can cause nephrotoxicity. Lithium (Eskalith, GlaxoSmithKline; Lithobid, Solvay Pharmaceuticals) is no longer recommended.

**Vasopressin-Receptor Antagonist Therapy**

A more recent option for treating SIAD is conivaptan (Vaprisol, Astellas Pharma), a vasopressin-receptor antagonist approved by the Food and Drug Administration in 2005 for intravenous treatment of euvolemic hyponatremia and approved in 2007 for intravenous treatment of hypervolemic hyponatremia (Table 3). In a double-blind, randomized trial, in patients assigned to conivaptan for 4 days, as compared with those assigned to placebo, the serum sodium levels increased by 6 mmol per liter. Although hypotension has not been reported in association with conivaptan, it is a risk, because conivaptan is a nonselective vasopressin-receptor antagonist; blocking the vasopressin V₁ receptor induces vasodilation. Currently, conivaptan use is limited to the treatment of hospitalized patients; it might be considered particularly for those who have moderate-to-severe hyponatremia and symptoms but not seizures, delirium, or coma, which would warrant the use of hypertonic saline. Infusion-site reactions are common (occurring in...
as many as 50% of patients, according to the package insert for the drug), and its metabolism by the 3A4 isoform of cytochrome P450 (CYP3A4) can result in drug interactions.

Although not yet clinically available, oral vasopressin-receptor antagonists that are selective for the vasopressin V2 receptor have been developed (Table 3). In two randomized, controlled trials of tolvaptan, serum sodium levels rose from a mean baseline level of 129 mmol per liter within 24 hours after the administration of the first dose of active drug and remained significantly higher (by 4 mmol per liter) than the levels in the placebo group (P<0.001) 30 days after the start of treatment.4 The tolvaptan group also had a clinically and statistically significant improvement in the mental component of the Medical Outcomes Study 12-item Short-Form General Health Survey (P=0.02). In an open-label study, in patients with SIAD, another long-acting oral vasopressin-receptor antagonist, satavaptan (Sanofi-Aventis), maintained serum sodium levels within the normal range (135 to 147 mmol per liter) at 1 year, without major side effects.37 The appropriate clinical role of the vasopressin-receptor antagonists remains to be defined.

One theoretical concern is that vasopressin-receptor antagonists might increase serum sodium levels too rapidly, putting patients at risk for osmotic demyelination. To date, this complication has not been reported, but trials of these agents have involved very close monitoring and minimal or no water restriction. These agents frequently cause dry mouth and thirst,36 which stimulate water intake, slowing the rise in serum sodium levels. Use of these agents in practice would require similarly close monitoring of serum sodium levels.

### Table 3. Vasopressin-Receptor Antagonists.*

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose of Drug</th>
<th>Vasopressin Receptor</th>
<th>Route of Administration</th>
<th>Urinary Volume</th>
<th>Urinary Osmolality</th>
<th>Sodium Excretion over 24 hr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conivaptan (Vaprisol, Astellas Pharma)†</td>
<td>20–40 mg daily</td>
<td>V1A and V2</td>
<td>Intravenous</td>
<td>Increased</td>
<td>Decreased</td>
<td>No change</td>
</tr>
<tr>
<td>Tolvaptan (Otsuka)</td>
<td>15–60 mg daily</td>
<td>V2</td>
<td>Oral</td>
<td>Increased</td>
<td>Decreased</td>
<td>No change</td>
</tr>
<tr>
<td>Lixivaptan (CardioKine)</td>
<td>100–200 mg</td>
<td>V2</td>
<td>Oral</td>
<td>Increased</td>
<td>Decreased</td>
<td>No change with low dose; increased with high dose</td>
</tr>
<tr>
<td>Satavaptan (Sanofi-Aventis)</td>
<td>12.5–50 mg</td>
<td>V2</td>
<td>Oral</td>
<td>Increased</td>
<td>Decreased</td>
<td>No change</td>
</tr>
</tbody>
</table>

* Data are adapted from Lee et al.35
† Conivaptan was approved for clinical use in 2005 by the Food and Drug Administration.

### Areas of Uncertainty

#### Optimal Strategies for Correcting Serum Sodium Levels

There are no data from randomized trials to guide optimal strategies for correction of serum sodium levels in patients with either acute or chronic hyponatremia, and the relative risks of osmotic demyelination and of hyponatremic encephalopathy continue to be debated.24 Acute symptomatic hyponatremia is routinely treated with hypertonic saline; many authorities recommend concomitant use of furosemide. Although some suggest that complete correction may be safe,33 others note that osmotic demyelination might occur even in this setting25 and recommend that correction with 3% saline during the first 24 hours be limited to 8 to 12 mmol per liter.9 In patients with seizure and coma, it is reasonable to use 3% saline at a rate of 1 to 2 mmol per liter per hour, even if the hyponatremia has been present for longer than 24 hours, keeping the maximal correction to 8 to 12 mmol per liter per day.1,9,10,25,27,33 When milder symptoms are present, correction is generally slower (rate, 0.5 mmol per liter per hour); some authorities avoid the use of 3% saline in this setting.

The best method for determining an initial rate for hypertonic saline infusion is also controversial.36; Table 4 presents some suggested strategies. The traditional approach is to estimate a sodium deficit and is not physiologically based, because SIAD is characterized by a water excess, rather than a sodium deficit. Another approach is to calculate the effect of 1 liter of an infusate on the serum sodium level, then estimate the volume needed for infusion; this formula predicts actual changes in the serum sodium level reasonably well,38 but it involves two calculations, which can
be confusing. Other formulas incorporate amounts of salt and water infused and excreted\(^5\)\(^6\); these add precision, but at the price of complexity. A simpler strategy that results in similar infusion rates is to infuse 3% saline (513 mmol per liter) at a rate of 1 to 2 ml per kilogram of body weight per hour\(^6\) to increase the serum sodium level by 1 to 2 mmol per liter per hour; twice this infusion rate (2 to 4 ml per kilogram per hour) may be used for a limited period in patients with coma or seizures; half the rate (0.5 ml per kilogram per hour) should be used if symptoms are mild.\(^6\) Many authorities recommend using furosemide (20 to 40 mg intravenously) with saline because it promotes free-water excretion and prevents extracellular-fluid volume expansion. Loop diuretics also increase the rate of increase in the serum sodium level. The rate of change in serum sodium levels must be monitored every 2 to 3 hours, and the infusion adjusted as needed.

**Osmotic Demyelination**

When symptoms of osmotic demyelination develop during the treatment of hyponatremia, case reports suggest that it may be possible to reverse the neurologic deficits by again lowering the serum sodium level. In two patients who had neurologic symptoms after rapid correction of serum sodium levels,\(^41\)\(^42\) symptoms diminished when serum sodium levels were modestly reduced by administering the vasopressin analogue desmopressin (DDAVP, Rhone–Poulenc Rorer; Stimate, Centeon) and 5% dextrose.

**Cerebral Salt Wasting**

SIAD may be difficult to distinguish from cerebral salt wasting, a syndrome of hyponatremia and extracellular-fluid volume depletion in patients with insults to the central nervous system.\(^43\)\(^44\) The primary feature that differentiates cerebral salt wasting from SIAD is extracellular-fluid volume depletion, but clinical assessment of volume status is imprecise.\(^18\)\(^45\) In a study that used central venous pressure (<5 cm of water) to differentiate these conditions in patients with subarachnoid hemorrhage and hyponatremia, 63% of cases were attributed to SIADH, and only 6.5% to salt wasting.\(^46\) Although cerebral salt wasting may be less common than is often suggested,\(^45\) many physicians favor the use of saline infusion rather than fluid restric-
tion for patients who have hyponatremia with subarachnoid hemorrhage, because of the risks associated with volume depletion in these patients.

PREVENTION OF POSTOPERATIVE HYponATREMIA

Surgical procedures typically increase circulating levels of arginine vasopressin; nevertheless, hypotonic intravenous fluids are frequently administered perioperatively.47 Most authorities recommend 0.9% sodium chloride in adults during the perioperative period, as long as hyponatremia is not present.48,49

GUIDELINES FROM PROFESSIONAL SOCIETIES

There are no professional guidelines for evaluating and treating SIAD.

SUMMARY AND RECOMMENDATIONS

The patient described in the vignette apparently has chronic hyponatremia attributable to SIAD; she has no neurologic symptoms. Treating the underlying cause (in this case, small-cell lung cancer) is the definitive means of correcting the hyponatremia. In the absence of symptoms, gradual correction of the hyponatremia is appropriate and should involve adequate solute intake (including salt and protein) and fluid restriction, starting at 500 ml per day of water (on the basis of the formula shown in Fig. 2). If the patient were disoriented, we would recommend increasing her serum sodium level by 0.5 to 1 mmol per liter per hour for a total of 8 mmol per liter during the first day. This increase can be accomplished by promoting free-water excretion with the use of furosemide and replacing sodium and potassium losses with 0.9% saline. Alternatively, conivaptan might be used to increase the serum sodium level, although clinical experience with vasopressin-receptor antagonists remains very limited.

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Clinical Practice


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