CLINICAL PRACTICE

The Syndrome of Inappropriate Antidiuresis

David H. Ellison, M.D., and Tomas Berl, M.D.

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

From the Division of Nephrology and Hypertension and the Department of Physiology and Pharmacology, Oregon Health and Science University and Veterans Affairs Medical Center, Portland, OR (D.H.E.); and the Division of Renal Diseases and Hypertension, University of Colorado Health Sciences Center, Denver (T.B.). Address reprint requests to Dr. Ellison at the Division of Nephrology and Hypertension, Oregon Health and Science University, PP262, 3314 SW U.S. Veterans Hospital Rd., Portland, OR 97239, or at ellisond@ohsu.edu.

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.[1] Mild hyponatremia (serum sodium, <135 mmol per liter) occurs in 15 to 22% of these patients and in approximately 7% of ambulatory patients[2]; moderate hyponatremia (serum sodium, <130 mmol per liter) occurs in 1 to 7% of hospitalized patients.[3,4] 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.[5] SIADH was first described in patients with bronchogenic carcinoma in whom a physiologic stimulus for the release of the antidiuretic hormone was lacking.[6] 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[7] (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.[8] 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.[8] 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.[4] 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 SIADH,[9,10] whereas others do not include them in this category.[11]

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.[12] The threshold serum sodium levels at which neurologic complications occur appear to be higher among women than among men.[13]

STRATEGIES AND EVIDENCE

DIAGNOSIS

Formal criteria for the diagnosis of SIAD are summarized in Table 2.[14] 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.[15] 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.[16] (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 tonicity) is equal to the
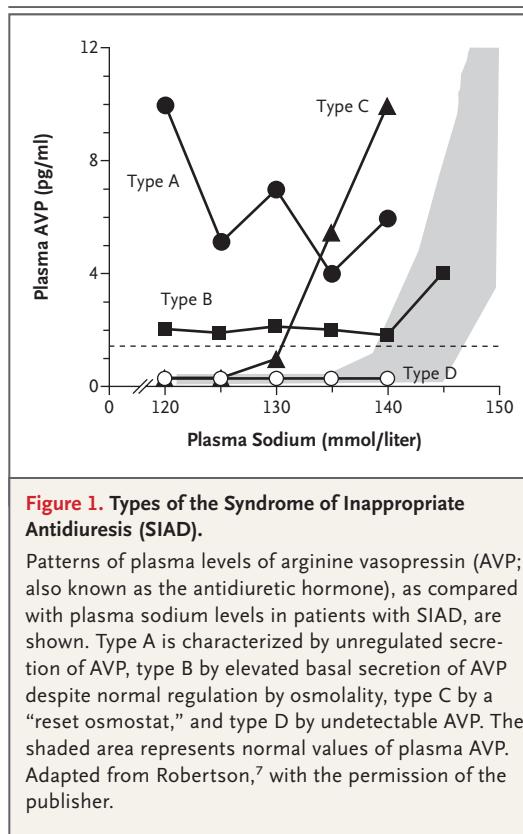

Figure 1. Types of the Syndrome of Inappropriate Antidiuresis (SIAD).

Patterns of plasma levels of arginine vasopressin (AVP; also known as the antidiuretic hormone), as compared with plasma sodium levels in patients with SIAD, are shown. Type A is characterized by unregulated secretion of AVP, type B by elevated basal secretion of AVP despite normal regulation by osmolality, type C by a "reset osmostat," and type D by undetectable AVP. The shaded area represents normal values of plasma AVP. Adapted from Robertson,[7] with the permission of the publisher.

measured osmolality minus (blood urea nitrogen ÷2.8), with blood urea nitrogen measured in milligrams per deciliter.[17] 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 euvolemia 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[18]; 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

Table 1. Causes of the Syndrome of Inappropriate Antidiuresis (SIAD).*

Malignant Diseases	Pulmonary Disorders	Disorders of the Central Nervous System	Drugs	Other Causes
Carcinoma	Infections	Infection	Drugs that stimulate release of AVP or enhance its action	Hereditary (gain-of-function mutations in the vasopressin V_2 receptor)
Lung	Bacterial pneumonia	Encephalitis	Chlorpropramide	Idiopathic
Small-cell	Viral pneumonia	Meningitis	SSRIs	Transient
Mesothelioma	Pulmonary abscess	Brain abscess	Tricyclic antidepressants	Endurance exercise
Oropharynx	Tuberculosis	Rocky Mountain spotted fever	Clofibrate (Atromid-S, Wyeth–Ayerst)	General anesthesia
Gastrointestinal tract	Aspergillosis	AIDS	Carbamazepine (Epitol, Lemmon; Tegretol, Ciba–Geigy)	Nausea
Stomach	Asthma	Bleeding and masses	Vincristine (Oncovin, Lilly; Vincasar, Pharmacia and Upjohn)	Pain
Duodenum	Cystic fibrosis	Subdural hematoma	Nicotine	Stress
Pancreas	Respiratory failure associated with positive-pressure breathing	Subarachnoid hemorrhage	Narcotics	
Genitourinary tract		Cerebrovascular accident	Antipsychotic drugs	
Ureter		Brain tumors	Ifosfamide (Ifex, Bristol-Myers Squibb)	
Bladder		Head trauma	Cyclophosphamide (Cytoxan, Bristol-Myers Squibb; Neosar, Pharmacia and Upjohn)	
Prostate		Hydrocephalus	Nonsteroidal antiinflammatory drugs	
Endometrium		Cavernous sinus thrombosis	MDMA ("ecstasy")	
Endocrine thymoma		Other	AVP analogues	
Lymphomas		Multiple sclerosis	Desmopressin (DDAVP, Rhone–Poulenc Rorer; Stimate, Centeon)	
Sarcomas		Guillain–Barré syndrome	Oxytocin (Pitocin, Parke–Davis; Syntocinon, Novartis)	
Ewing's sarcoma		Shy–Drager syndrome	Vasopressin	
		Delirium tremens		
		Acute intermittent porphyria		

* AIDS denotes the acquired immunodeficiency syndrome, AVP arginine vasopressin, SSRI selective serotonin-reuptake inhibitor, and MDMA 3,4-methylenedioxymethamphetamine.

with hyponatremia suggest SIAD, but are not diagnostic[5]; 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%.[19-21] 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.[18,22]

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[17,22,23]; 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).[11,24,25] For symptomatic patients with severe hyponatremia known to have developed within 48 hours, clinical experience suggests that rapid treatment is warranted.[26] 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.[1] Many authorities recommend concomitant furosemide,[1] although some recommend avoiding it[10] or reserving it for patients with extracellular-fluid volume expansion.[9,27] 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.[1,9,27] One approach is to aim for the cessation of neurologic symptoms, such as seizures, and then reduce the correction rate.[25] An increase in serum sodium levels of less than 10 mmol per liter is usually sufficient to reduce the symptoms and prevent complications.[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[29]; others suggest that rapid correction increases morbidity or mortality.[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.[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.[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)[25] is recommended to avoid overcorrection. Some authorities recommend brain imaging

Table 2. Diagnosis of SIAD.*
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.[6] and Janicic and Verbalis.[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.

(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.[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.[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.[6,33] 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
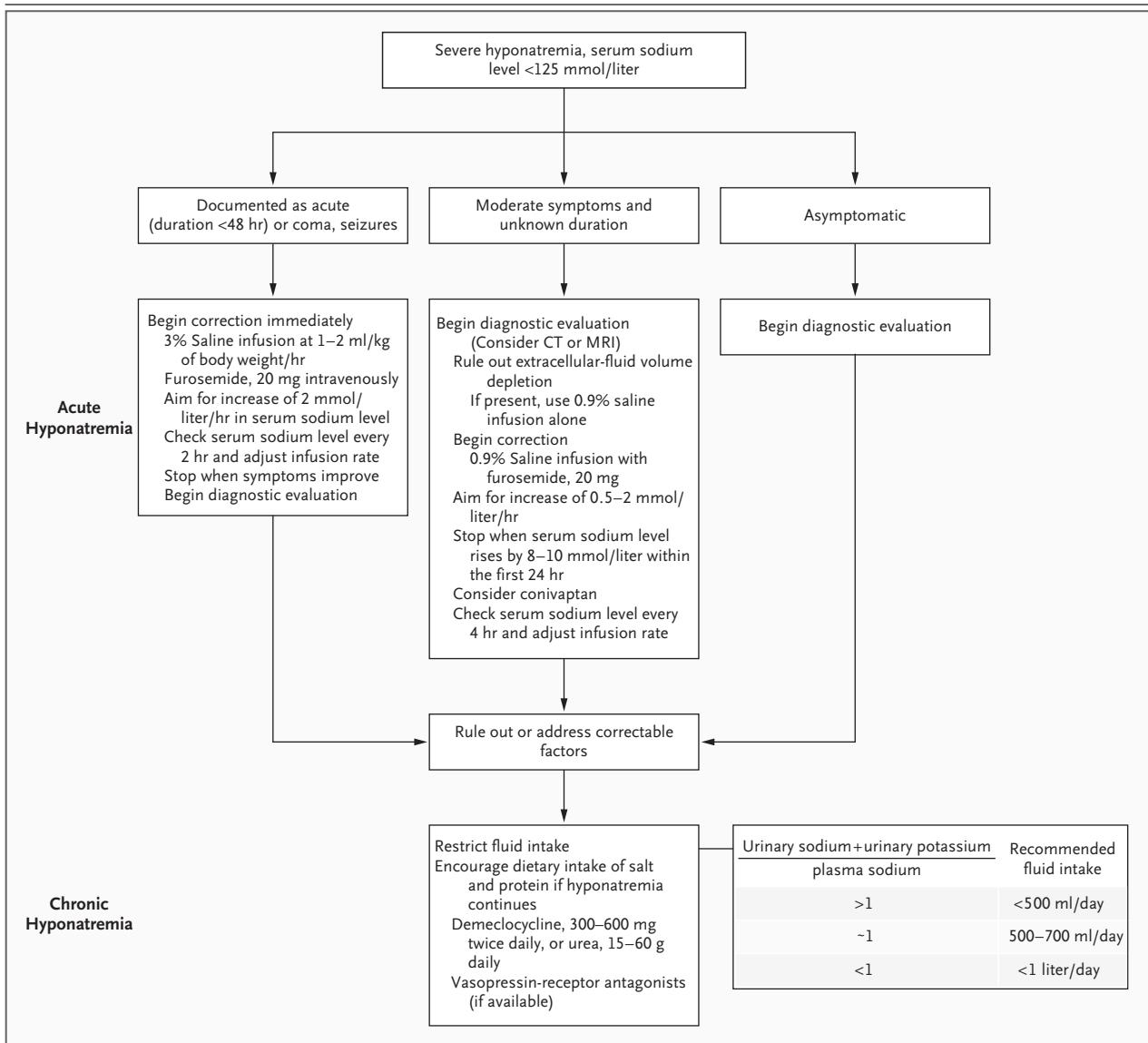
Severe hyponatremia, serum sodium level <125 mmol/liter

Documented as acute (duration <48 hr) or coma, seizures

Moderate symptoms and unknown duration

Asymptomatic

Acute Hyponatremia

Begin correction immediately
  3% Saline infusion at 1–2 ml/kg of body weight/hr
  Furosemide, 20 mg intravenously
  Aim for increase of 2 mmol/liter/hr in serum sodium level
  Check serum sodium level every 2 hr and adjust infusion rate
  Stop when symptoms improve
  Begin diagnostic evaluation

Begin diagnostic evaluation
  (Consider CT or MRI)
  Rule out extracellular-fluid volume depletion
    If present, use 0.9% saline infusion alone
  Begin correction
    0.9% Saline infusion with furosemide, 20 mg
  Aim for increase of 0.5–2 mmol/liter/hr
  Stop when serum sodium level rises by 8–10 mmol/liter within the first 24 hr
  Consider conivaptan
  Check serum sodium level every 4 hr and adjust infusion rate

Begin diagnostic evaluation

Rule out or address correctable factors

Chronic Hyponatremia

Restrict fluid intake
  Encourage dietary intake of salt and protein if hyponatremia continues
  Demeclocycline, 300–600 mg twice daily, or urea, 15–60 g daily
  Vasopressin-receptor antagonists (if available)

$\dfrac{\text{Urinary sodium} + \text{urinary potassium}}{\text{plasma sodium}}$	Recommended fluid intake
>1	<500 ml/day
~1	500–700 ml/day
<1	<1 liter/day

Figure 2. Algorithm for the Treatment of Hyponatremia Associated with SIAD.

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[34] and approved in 2007 for intravenous treatment of hypervolemic hyponatremia[35] (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 V_1 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

Table 3. Vasopressin-Receptor Antagonists.*						
Drug	Dose of Drug	Vasopressin Receptor	Route of Administration	Urinary Volume	Urinary Osmolality	Sodium Excretion over 24 hr
Conivaptan (Vaprisol, Astellas Pharma)†	20–40 mg daily	V_{1A} and V_2	Intravenous	Increased	Decreased	No change
Tolvaptan (Otsuka)	15–60 mg daily	V_2	Oral	Increased	Decreased	No change
Lixivaptan (CardioKine)	100–200 mg	V_2	Oral	Increased	Decreased	No change with low dose; increased with high dose
Satavaptan (Sanofi-Aventis)	12.5–50 mg	V_2	Oral	Increased	Decreased	No change

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

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 V_2 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[36] (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.

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 setting[25] 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)[9]; 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[38]; 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

Table 4. Formulas for Calculating Initial Saline Infusion Rates.*

Source	Step 1	Step 2	Example of Rate (ml/hr)
Traditional[1]	Na required $= TBW \times ([Na]_2 - [Na]_1)$	$\text{Volume (liter)} = \dfrac{\text{Na required (mmol)}}{513 \text{ mmol/liter}}$	82
Adrogué and Madias[1]	$\Delta[Na]_S \text{ (with 1 liter)} = \dfrac{[Na]_{inf} - [Na]_1}{TBW + 1}$	$\text{Volume (liter)} = \dfrac{\text{Desired } \Delta[Na]_S}{\Delta[Na]_S \text{(with 1 liter)}}$	107
Barsoum and Levine[39]	$\Delta[Na]_S = \dfrac{(V_{inf})[Na]_{inf} - (V_u)[E]_{urine} - (\Delta V)[Na]_1}{TBW + \Delta V}$	$\text{Volume (liter)} = \dfrac{\text{Desired } \Delta[Na]_S}{\Delta[Na]_S \text{ (with 1 liter)}}$	107
Nguyen and Kurtz[40]		$\text{Volume (liter)} = \dfrac{TBW \times \left(1 - \dfrac{[Na]_1 + 23.8}{[Na]_2 + 23.8}\right) + V_{input} - \dfrac{[E]_{input} \times V_{input}}{[E]_{urine}}}{\dfrac{[E]_{inf}}{[E]_{urine}} - 1}$	90
Janicic and Verbalis[9]		Rate (ml/hr) is the goal rate of $[Na]_S$ rise (mmol/liter/hr) per kg of body weight	70

* The examples assume a body weight of 70 kg, current serum sodium ($[Na]_S$) level of 110 mmol per liter, desired $[Na]_S$ level of 120 mmol per liter, total body water (TBW) of 42 liters, time of 10 hours, urinary volume of 1 liter, urinary sodium level of 80 mmol per liter, urinary potassium level of 40 mmol per liter, and treatment fluid (infusion) of 513 mmol per liter, where $[Na]_1$ is the current $[Na]_S$ and $[Na]_2$ represents the $[Na]_S$ level desired after treatment, $\Delta[Na]_S = [Na]_2 - [Na]_1$; $[E]$ is $[Na] + [K]$. If the actual rate of correction is different from that predicted, it may be useful to calculate the electrolyte-free water clearance, to help guide treatment. The electrolyte-free water clearance is calculated as

$$C^e_{H_2O} = V\left(1 - \frac{U_{Na} + U_K}{P_{Na}}\right),$$

where $C^e_{H_2O}$ denotes electrolyte-free water clearance, U_{Na} urinary sodium, U_K urinary potassium, and P_{Na} plasma sodium. If the clearance value is greater than 0, then ongoing losses of free water are contributing to the rise in $[Na]_S$. In all cases, the formulas are used only to estimate the initial infusion rate; the rate must be adjusted on the basis of the measured rate of the rise in serum sodium. Inf denotes infused fluid.

be confusing. Other formulas incorporate amounts of salt and water infused and excreted[39,40]; 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[9] 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.[9] 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 neu-rologic 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,[45,46] 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 hypernatremia 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.

REFERENCES

1. Adrogue HJ, Madias NE. Hyponatremia. N Engl J Med 2000;342:1581-9.
2. Hawkins RC. Age and gender as risk factors for hyponatremia and hypernatremia. Clin Chim Acta 2003;337:169-72.
3. Anderson RJ, Chung H-M, Kluge R, Schrier RW. Hyponatremia: a prospective analysis of its epidemiology and the pathogenetic role of vasopressin. Ann Intern Med 1985;102:164-8.
4. Upadhyay A, Jaber BL, Madias NE. Incidence and prevalence of hyponatremia. Am J Med 2006;119:Suppl 1:S30-S35.
5. Berghmans T, Paesmans M, Body JJ. A prospective study on hyponatraemia in medical cancer patients: epidemiology, aetiology and differential diagnosis. Support Care Cancer 2000;8:192-7.
6. Schwartz WB, Bennett W, Curelop S, Bartter FC. A syndrome of renal sodium loss and hyponatremia probably resulting from inappropriate secretion of antidiuretic hormone. Am J Med 1957;23:529-42.
7. Robertson GL. Regulation of arginine vasopressin in the syndrome of inappropriate antidiuresis. Am J Med 2006;119: Suppl 1:S36-S42.
8. Feldman BJ, Rosenthal SM, Vargas GA, et al. Nephrogenic syndrome of inappropriate antidiuresis. N Engl J Med 2005; 352:1884-90.
9. Janicic N, Verbalis JG. Evaluation and management of hypo-osmolality in hospitalized patients. Endocrinol Metab Clin North Am 2003;32:459-81.
10. Smith DM, McKenna K, Thompson CJ. Hyponatraemia. Clin Endocrinol (Oxf) 2000;52:667-78.
11. Chonchol M, Berl M. Hyponatremia. In: DuBose TD Jr, Hamm LL, eds. Acid-base and electrolyte disorders: a companion to Brenner & Rector's The Kidney. Philadelphia: Saunders, 2002:229-39.
12. Renneboog B, Musch W, Vandemergel X, Manto MU, Decaux G. Mild chronic hyponatremia is associated with falls, unsteadiness, and attention deficits. Am J Med 2006;119:e1-e8.
13. Arieff AI. Influence of hypoxia and sex on hyponatremic encephalopathy. Am J Med 2006;119:Suppl 1:S59-S64.
14. Saeed BO, Beaumont D, Handley GH, Weaver JU. Severe hyponatraemia: investigation and management in a district general hospital. J Clin Pathol 2002;55:893-6.
15. Turchin A, Seifter JL, Seely EW. Mind the gap. N Engl J Med 2003;349:1465-9. [Erratum, N Engl J Med 2004;350:629.]
16. Hillier TA, Abbott RD, Barrett EJ. Hyponatremia: evaluating the correction factor for hyperglycemia. Am J Med 1999;106:399-403.
17. Milionis HJ, Liamis GL, Elisaf MS. The hyponatremic patient: a systematic approach to laboratory diagnosis. CMAJ 2002;166:1056-62.
18. Chung H-M, Kluge R, Schrier RW, Anderson RJ. Clinical assessment of extracellular fluid volume in hyponatremia. Am J Med 1987;83:905-8.
19. Musch W, Decaux G. Utility and limitations of biochemical parameters in the evaluation of hyponatremia in the elderly. Int Urol Nephrol 2001;32:475-93.
20. Passamonte PM. Hypouricemia, inappropriate secretion of antidiuretic hormone, and small cell carcinoma of the lung. Arch Intern Med 1984;144:1569-70.
21. Beck LH. Hypouricemia in the syndrome of inappropriate secretion of antidiuretic hormone. N Engl J Med 1979;301: 528-30.
22. Musch W, Thimpont J, Vandervelde D, Verhaeverbeke I, Berghmans T, Decaux G. Combined fractional excretion of sodium and urea better predicts response to saline in hyponatremia than do usual clinical and biochemical parameters. Am J Med 1995;99:348-55.
23. Musch W, Decaux G. Treating the syndrome of inappropriate ADH secretion with isotonic saline. QJM 1998;91:749-53.
24. Berl T. Treating hyponatremia: what is all the controversy about? Ann Intern Med 1990;113:417-9.
25. Decaux G, Soupart A. Treatment of symptomatic hyponatremia. Am J Med Sci 2003;326:25-30.
26. Ayus JC, Krothapalli RK, Arieff AI. Treatment of symptomatic hyponatremia and its relation to brain damage: a prospective study. N Engl J Med 1987;317:1190-5.
27. Palmer BF, Gates JR, Lader M. Causes and management of hyponatremia. Ann Pharmacother 2003;37:1694-702.
28. Lauriat SM, Berl T. The hyponatremic patient: practical focus on therapy. J Am Soc Nephrol 1997;8:1599-607.

29. Ayus JC, Arieff AI. Chronic hyponatremic encephalopathy in postmenopausal women: association of therapies with morbidity and mortality. JAMA 1999;281:2299-304.

30. Sterns RH. The treatment of hyponatremia: first, do no harm. Am J Med 1990;88:557-60.

31. Laureno R, Karp BI. Myelinolysis after correction of hyponatremia. Ann Intern Med 1997;126:57-62.

32. Gross P, Reimann D, Henschkowski J, Damian M. Treatment of severe hyponatremia: conventional and novel aspects. J Am Soc Nephrol 2001;12:Suppl 17:S10-S14.

33. Thurman JM, Halterman TJ, Berl T. Therapy of dysnatremic disorders. In: Brady HR, Wilcox CS, eds. Therapy in nephrology and hypertension: a companion to Brenner & Rector's The Kidney. 2nd ed. London: Saunders, 2003:335-48.

34. Ghali JK, Koren MJ, Taylor JR, et al. Efficacy and safety of oral conivaptan: a V_{1A}/V_2 vasopressin receptor antagonist, assessed in a randomized, placebo-controlled trial in patients with euvolemic or hypervolemic hyponatremia. J Clin Endocrinol Metab 2006;91:2145-52.

35. Lee CR, Watkins M, Patterson JH, et al. Vasopressin: a new target for the treatment of heart failure. Am Heart J 2003;146:9-18.

36. Schrier RW, Gross P, Gheorghiade M, et al. Tolvaptan, a selective oral vasopressin V2-receptor antagonist, for hyponatremia. N Engl J Med 2006;355:2099-112.

37. Soupart A, Gross P, Legros J-J, et al. Successful long-term treatment of hyponatremia in syndrome of inappropriate antidiuretic hormone secretion with SR 121 463 B, an orally active, nonpeptide, vasopressin V-2 receptor antagonist. J Am Soc Nephrol 2004;15:563A. abstract.

38. Liamis G, Kalogirou M, Saugos V, Elisaf M. Therapeutic approach in patients with dysnatraemias. Nephrol Dial Transplant 2006;21:1564-9.

39. Barsoum NR, Levine BS. Current prescriptions for the correction of hyponatraemia and hypernatraemia: are they too simple? Nephrol Dial Transplant 2002;17:1176-80.

40. Nguyen MK, Kurtz I. New insights into the pathophysiology of the dysnatremias: a quantitative analysis. Am J Physiol Renal Physiol 2004;287:F172-F180.

41. Soupart A, Ngassa M, Decaux G. Therapeutic relowering of the serum sodium in a patient after excessive correction of hyponatremia. Clin Nephrol 1999;51:383-6.

42. Oya S, Tsutsumi K, Ueki K, Kirino T. Reinduction of hyponatremia to treat central pontine myelinolysis. Neurology 2001;57:1931-2.

43. Diringer MN, Zazulia AR. Hyponatremia in neurologic patients: consequences and approaches to treatment. Neurologist 2006;12:117-26.

44. Tisdall M, Crocker M, Watkiss J, Smith M. Disturbances of sodium in critically ill adult neurologic patients: a clinical review. J Neurosurg Anesthesiol 2006;18:57-63.

45. Singh S, Bohn D, Carlotti AP, Cusimano M, Rutka JT, Halperin ML. Cerebral salt wasting: truths, fallacies, theories, and challenges. Crit Care Med 2002;30:2575-9.

46. Sherlock M, O'Sullivan E, Agha A, et al. The incidence and pathophysiology of hyponatraemia after subarachnoid haemorrhage. Clin Endocrinol (Oxf) 2006;64:250-4.

47. Way C, Dhamrait R, Wade A, Walker I. Perioperative fluid therapy in children: a survey of current prescribing practice. Br J Anaesth 2006;97:371-9.

48. Holliday MA, Friedman AL, Segar WE, Chesney R, Finberg L. Acute hospital-induced hyponatremia in children: a physiologic approach. J Pediatr 2004;145:584-7.

49. Moritz ML, Ayus JC. Prevention of hospital-acquired hyponatremia: a case for using isotonic saline. Pediatrics 2003;111:227-30.

Copyright © 2007 Massachusetts Medical Society.

**RECEIVE IMMEDIATE NOTIFICATION WHEN
A *JOURNAL* ARTICLE IS RELEASED EARLY**

To be notified when an article is released early
on the Web and to receive the table of contents
of the *Journal* by e-mail every Wednesday evening,
sign up through our Web site at
www.nejm.org