HYPONATREMIA AND HYPERNATREMIA

Linda F. Fried, MD, and Paul M. Palevsky, MD

Hyponatremia and hypernatremia are common electrolyte disorders and are associated with increased morbidity and mortality.\(^5\) Under normal circumstances, the plasma sodium concentration is maintained within a narrow range despite wide variations in sodium and water intake. This is achieved through an integration of thirst, vasopressin (antidiuretic hormone) secretion, and renal responsiveness to vasopressin. This article provides a pathophysiologic approach to understanding the causes and management of hyponatremia and hypernatremia.

REGULATION OF BODY FLUID TONICITY

Sodium is the dominant cation in extracellular fluid and is the main determinant of plasma osmolality. Although it may range from 280 to 295 mmol/kg, plasma osmolality is remarkably constant for a given individual.\(^92\) Osmolality is determined by the ratio of solute content to water. If total body water changes without an accompanying change in total body solute, plasma osmolality changes, and hyponatremia or hypernatremia results. Disturbances of the plasma sodium concentration are therefore the result of alterations in water homeostasis. In contrast,

The views expressed herein are solely those of the authors and do not necessarily reflect those of the U.S. government.

From the Renal Section, Medical Service, VA Pittsburgh Health Care System; and the Renal Electrolyte Division, Department of Medicine, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania
disturbances of sodium homeostasis primarily affect extracellular fluid volume and may result in hypovolemia or hypervolemia. Although water homeostasis and sodium balance are independently regulated, there are strong interactions. Alterations in sodium balance, although not a direct cause of hypernatremia or hyponatremia, modulate water homeostasis and may contribute to the development of these disturbances.

An important distinction must also be made between the physical property of osmolality and the biologic property of effective osmolality or tonicity. Body fluid osmolality is the measured concentration of all solutes per unit of water. Although water freely diffuses across biologic membranes, the majority of solutes are relatively impermeant and contribute to the osmotic forces distributing water across body fluid compartments. In situations in which the concentration of solute differs across membranes, water diffuses to restore osmotic equilibrium. In contrast, a few solutes (in particular urea) freely diffuse across most biologic membranes. These solutes, although contributing to body fluid osmolality, do not affect the distribution of water and are not included in the calculation of body fluid tonicity.

NORMAL WATER HOMEOSTASIS

Water Intake

At steady-state, water intake and losses are matched. Most fluid is ingested as liquid with the amount determined primarily by social or habitual custom. In addition, approximately 750 mL is ingested reformed in solid food, and 350 mL is generated through metabolism. Dietary water intake is usually greater than obligate water losses. However, if water losses increase and exceed normal intake, thirst is stimulated and water ingestion increases.

Thirst is physiologically regulated, in response to changes in body fluid tonicity and extracellular volume. Thirst osmoreceptors are located in the organum vasculosum of the lamina terminalis (OVLT) in the anterior wall of the third ventricle. These receptors, which are in proximity to but anatomically distinct from the osmoreceptors that regulate vasopressin secretion, stimulate thirst as body fluid osmolality rises above a threshold of approximately 290 to 295 mmol/kg. In response to increases in osmolality above this threshold, thirst increases linearly. Thirst is also stimulated by hypovolemia and hypotension. Direct neural activation as well as systemic and intracerebral activation of angiotensin II stimulates receptors in the OVLT and subfornical organs in the hypothalamus and induce drinking. In contrast to the response to hypertonicity, the response to volume depletion is nonlinear, and thirst is not stimulated unless the change in volume exceeds 10%.
Water Excretion

Water loss occurs via the skin and respiratory tract (insensible losses), gastrointestinal tract, and kidneys. Under normal conditions, insensible losses average 0.6 mL/kg/hour or approximately 1 L/day in adults. Insensible losses may be increased by burns, fever, tachypnea, exercise, and elevations in ambient temperature. Gastrointestinal water loss is normally less than 100 to 150 mL/day but can increase markedly in the setting of diarrhea, vomiting, nasogastric suction, and biliary or pancreatic drainage. Gastrointestinal and insensible losses are not subject to physiologic regulation. In contrast, the kidney regulates renal water loss in response to alterations in serum osmolarity and effective arterial volume. Urine volume can range from less than 500 mL to more than 20 L per day. Even in the setting of maximum renal water reabsorption, the obligate renal and extrarenal water loss is approximately 1 L/day. Thus, although renal water excretion provides the main defense against water depletion, renal water conservation alone is insufficient to defend against dehydration and hypertonicity. The ultimate defense against hypernatremia is the stimulation of thirst.

Renal Water Handling

The kidney filters approximately 150 L of isotonic glomerular filtrate daily. In the proximal tubule, approximately two thirds of this filtrate is isotonically reabsorbed, with the volume increasing to more than 80% of filtered load in states of effective arterial volume depletion. In the more distal segments of the nephron, water and electrolytes are independently reabsorbed (Fig. 1). In the descending loop of Henle, water is reabsorbed while solute is retained, ultimately raising the osmolality of the tubular fluid to approximately 1200 mmol/kg. The ascending limb of the loop of Henle and the distal tubule are relatively impermeable to water. In these segments, collectively referred to as the diluting segments, electrolytes are reabsorbed, progressively diluting the tubular fluid to a minimal osmolality of less than 50 mmol/kg. In the collecting duct, water reabsorption is modulated by vasopressin. In response to hypotonicity, vasopressin secretion is suppressed, the water permeability of the collecting duct is low, and a dilute urine is excreted. During hypertonicity, vasopressin secretion is stimulated, increasing the permeability of the collecting duct, permitting water reabsorption, and ultimately resulting in the excretion of a concentrated urine. Because water reabsorption varies as a continuous function of circulating vasopressin levels, urine osmolality can be precisely regulated, varying from less than 100 mmol/kg to 800 to 1200 mmol/kg.

Conceptually, renal water handling can be separated into three interrelated processes: (1) the delivery of fluid to the diluting segments of the nephron, (2) the separation of solute and water in the diluting segment, and (3) the variable reabsorption of water in the collecting
Figure 1. The renal handling of water. Open arrows represent water and solid arrows represent electrolytes. Water and electrolytes are filtered by the glomerulus. In the proximal tubule (1), water and electrolytes are absorbed isotonically. In the descending loop of Henle (2), water is absorbed to achieve osmotic equilibrium with the interstitium while electrolytes are retained. The numbers between the descending and ascending limbs represent the osmolality of the interstitium. The delivery of solute and fluid to the distal nephron is a function of proximal tubular reabsorption; as proximal tubular reabsorption increases, delivery of solute to the medullary (3a) and cortical (3b) diluting site decreases. In the diluting sites, electrolyte-free water is generated through selective reabsorption of electrolytes while water is retained in the tubular lumen, generating a dilute tubular fluid. In the absence of vasopressin (4a), the collecting duct remains relatively impermeable to water and a dilute urine is excreted. When vasopressin is present (4b), water is reabsorbed from these vasopressin-responsive nephron segments, allowing the excretion of a concentrated urine.

duct. The first two processes occur independently of both body fluid osmolality and the final urine volume and composition. In contrast, collecting duct water reabsorption is tightly regulated on the basis of body fluid osmolality and is the final arbiter of both urine volume and concentration.

Determinants of Maximal Urinary Dilution and Concentration

Maximal urinary dilution requires (1) delivery of an adequate volume of fluid to the diluting segments of the nephron, (2) generation of maximally hypotonic fluid in the diluting segments, and (3) maintenance of water impermeability of the collecting duct.

Delivery to the diluting segment is influenced by the glomerular filtration rate (GFR) and proximal tubular function. Reductions in GFR and states associated with increased proximal tubular fluid reabsorption
(e.g., volume depletion, congestive heart failure, cirrhosis, and nephrotic syndrome) decrease the delivery of fluid out of the proximal tubule and limit free water generation in the diluting segments. Impairment of electrolyte transport in the diluting segments, as may occur in interstitial renal disease or as the result of pharmacologic therapy with thiazide or loop-acting diuretics, increases the minimal achievable tubular fluid osmolality and also restricts free water generation. Maintenance of the water permeability of the collecting duct requires suppression of vasopressin secretion. Hemodynamically mediated or inappropriate vasopressin secretion contributes to the development of hyponatremia in the majority of patients. In addition, vasopressin-independent water reabsorption increases in any circumstance in which delivery of fluid to the collecting duct and collecting duct flow rate are decreased.

Maximal urinary concentration requires the generation and maintenance of the corticopapillary interstitial concentration gradient and the utilization of this gradient for the reabsorption of water from the collecting duct. The interstitial concentration gradient, which increases from isotonicity at the corticomedullary junction to approximately 1200 mmol/kg at the papillary tip, is generated by the countercurrent multiplier effect of the loop of Henle. The normal function of this countercurrent multiplier is dependent on adequate delivery of fluid to the thick ascending limb of the loop of Henle and the accumulation of solute in the medullary interstitium. The major accumulated solutes are sodium and chloride, which are actively transported into the interstitium from the thick ascending limb, and urea, which is reabsorbed from the medullary collecting duct. Maintenance of the concentration gradient requires that water reabsorbed from the collecting duct be returned to the systemic circulation, while solute remains trapped in the medullary interstitium. This is accomplished through the organization of the medullary circulation (the vasa recta) as a countercurrent exchanger. Any process that disrupts either the generation or the maintenance of the interstitial gradient impairs urinary concentration. These include interstitial renal disease, use of loop-acting diuretics, protein malnutrition (which results in decreased urea generation), states of osmotic diuresis, and other states of high urinary flow.

The use of the interstitial osmotic gradient is dependent on the action of vasopressin on the collecting duct. In response to vasopressin, the water permeability of the collecting duct increases, permitting progressive extraction of water until, at the papilla, the tubular fluid (urine) approaches osmotic equilibrium with the renal papillary interstitium (1000 to 1200 mmol/kg). Thus, for maximal urinary concentration to be achieved, both vasopressin secretion and collecting duct responsiveness to vasopressin must be normal.

Regulation of Renal Water Excretion

Renal water excretion is under the direct control of the neurohypophyseal hormone vasopressin. Vasopressin is synthesized in the
supraoptic and paraventricular nuclei of the hypothalamus. After synthesis, it is transported down axons terminating in the posterior pituitary, where it is stored and secreted. The primary stimulus for vasopressin release is an increase in plasma osmolality. As with thirst, there is a set-point above which vasopressin secretion is stimulated. This set-point is slightly lower than that for thirst and averages 280 to 285 mmol/kg. Above this level, the rise in vasopressin is linear and steep. A change in plasma osmolality of only 1% leads to an increase in vasopressin of approximately 1 pg/mL, with maximum antidiuresis occurring at a vasopressin concentration of 5 pg/mL. Vasopressin secretion is also stimulated by hypotension and volume depletion. The response to these stimuli, however, is curvilinear and does not occur until effective arterial volume is decreased by 8% to 10%. With greater decreases in effective arterial volume, vasopressin secretion rises exponentially. The response to volume changes does not eliminate responsiveness to osmotic stimuli but produces a shift in the slope of the curve and change in set-point (Fig. 2).

Vasopressin's main physiologic action is to modulate water reabsorption from the collecting duct. Vasopressin binds to V2-receptors

Rights were not granted to include this figure in electronic media. Please refer to the printed journal.

Figure 2. The effect of changes in blood volume or pressure on the osmoregulation of vasopressin. The numbers inside the circles indicate the magnitude of the hemodynamic change required to effect the shift in the corresponding regression line. (From Robertson GL, Shelton RL, Athar S: The osmoregulation of vasopressin. Kidney Int 10:25, 1976; with permission.)
along the basolateral membrane of collecting duct cells. Binding to the receptor activates intracellular adenylate cyclase, increasing the intracellular concentration of the second messenger cyclic adenosine monophosphate (AMP). Through a mechanism that remains to be completely elucidated, cyclic AMP stimulates the synthesis and insertion of the aquaporin-2 water channel into the luminal membrane of collecting duct cells, thereby increasing the water permeability of the collecting duct.

**Free Water Clearance**

Although urine osmolality provides a useful index of renal concentration and dilution, a complete assessment of renal water handling requires assessment of both osmolality and volume. It is therefore useful to divide the urine volume into two conceptual components: (1) a volume that is necessary to excrete urinary solute iso-osmotically to plasma and (2) a remaining volume that represents the solute-free water excreted (or reabsorbed). Because urea, the major nonelectrolyte solute in urine, does not contribute to tonicity, a more useful assessment of renal water handling may be made by evaluating electrolyte rather than total solute excretion. By analogy with solute-free water, electrolyte-free water is the volume of urine remaining after removing the volume necessary for urinary electrolytes (sodium and potassium along with their associated anions) to be isotonic to plasma. A positive value represents electrolyte-free water excretion, whereas a negative value represents free water reabsorption.

**HYPONATREMIA**

The reported incidence of hyponatremia ranges from 1% to 4% and is associated with a 7 to 60 fold increase in mortality. It is not clear, however, whether the excess mortality is directly related to the hyponatremia or whether the hyponatremia is merely a marker for severe underlying disease. Hyponatremia results when water intake exceeds water excretion. Because, under normal circumstances, the renal capacity for free water excretion is much greater than water intake, the development of hyponatremia is generally associated with impaired renal diluting capacity and nonosmotic vasopressin secretion.

**Causes**

The manifestations of hyponatremia primarily result from hypotonicity of body fluids. Because the intracellular solute content remains constant, hypotonicity results in the shift of water into the intracellular compartment and produces cell swelling. These changes in cell volume...
are of greatest significance in the brain, which is enclosed in the fixed calvarium. Although hypotonicity is always associated with hyponatremia, hyponatremia can also be seen in cases in which the serum osmolarity is normal or high. It is important to recognize these situations because their management differs from the management of hypotonicity.

**Normotonic Hyponatremia**

Hyponatremia not associated with a change in tonicity has been termed pseudohyponatremia. This disturbance, associated with extreme hyperlipidemia or hyperproteinemia, is actually a laboratory artifact and is dependent on the method used to measure the sodium concentration. Plasma is normally approximately 93% water and 7% non-aqueous components (lipids and proteins). Older laboratory tests using flame emission spectrophotometry calculated the sodium concentration based on the mass of sodium in a given volume of plasma or serum. If the aqueous portion of serum is decreased, the total content of sodium per unit volume of plasma is reduced, and although the concentration of sodium in the aqueous phase is normal, a falsely low reading is returned. Pseudohyponatremia is rarely seen today because the sodium concentration is more commonly measured using direct potentiometry. With this method, the sodium concentration is directly measured using a sodium-selective electrode and is not affected by changes in the relative proportion of aqueous and nonaqueous phases of plasma.

**Hypertonic Hyponatremia**

Hyponatremia can also develop in settings of hypertonicity. Increases in tonicity from the accumulation of an osmotically active non-electrolyte solute shifts water from the intracellular compartment to the extracellular fluid, thus diluting the plasma sodium concentration. This most commonly occurs during hyperglycemia. The change in the plasma sodium concentration varies in proportion to the degree of hyperglycemia. Although the relationship is not linear, the serum sodium concentration falls by approximately 1.6 mmol/L for each 100 mg/dL rise in glucose concentration. Other solutes that may produce hypertonic hyponatremia include mannitol, sorbitol, maltose, and radiocontrast. In these situations, the hyponatremia per se does not require treatment; however, the underlying hypertonic state must be identified and appropriately treated.

**Hypotonic Hyponatremia**

Hypotonic hyponatremia always reflects an inability of the kidney to excrete a sufficient volume of electrolyte-free water to match intake. These disorders can be divided pathophysiologically on the basis of effective arterial volume.
In the setting of decreased effective arterial volume, multiple regulatory systems are activated. Decreased stretch in the baroreceptors of the aortic arch and carotid body and stretch receptors in the great veins, pulmonary vasculature, and atria lead to increased sympathetic tone.98 This, along with decreased renal perfusion, leads to renin release and the formation of angiotensin II.98 The hemodynamic changes mediated by angiotensin ultimately increase proximal tubular reabsorption of sodium, decreasing delivery of solute to distal diluting segments and impairing free water generation. If the decrease in effective volume is of sufficient magnitude, vasopressin release is also stimulated, further impairing free water excretion.33 Angiotensin also increases thirst, stimulating water intake.39 If free water intake exceeds the kidney's reduced capacity to excrete it, hyponatremia occurs.

Decreased effective arterial volume may be secondary to true volume depletion, as in hemorrhage, third-space sequestration, or sodium depletion, or may be the consequence of cirrhosis, nephrosis, congestive heart failure, or severe hypoalbuminemia. In both settings, the pathophysiologic mechanisms leading to hyponatremia are the same. The propensity to develop hyponatremia in the setting of cirrhosis, nephrosis, or congestive heart failure is a function of the disorder's overall impact. For example, the development of hyponatremia in heart failure is associated with more severe cardiac impairment and portends a worse outcome.84

Euvolemic hyponatremia results from increases in total body water with only minimal change in total body sodium. In most cases, the increase in total body water produces a mild volume expansion and a mild natriuresis.77 The increase in extracellular volume is small, however, and the patients appear euvolemic on clinical examination.

In the setting of normal renal function, hyponatremia secondary to pure water intake is rare because the normal kidney can excrete in excess of 20 L/day of electrolyte-free water.90 Hyponatremia secondary to compulsive water drinking, however, occurs in 3% to 7% of institutionalized psychotic patients.56, 90 Although some of these patients had water intake greater than 20 L/day and presented with polyuria, hyponatremia, and a maximally dilute urine, most cases of hyponatremia in psychiatric patients are associated with some degree of nonosmotic vasopressin release and decreased free water clearance.47, 103, 115 Acute, iatrogenic water intoxication producing hyponatremia may occur following transurethral resection of the prostate as the result of absorption of large volumes of hypotonic irrigation fluids.88

Euvolemic hyponatremia is most commonly associated with nonosmotic vasopressin secretion.4 Included in this category are glucocorticoid deficiency, severe hypothyroidism, thiazide diuretic-associated hyponatremia, the syndrome of inappropriate secretion of antidiuretic hormone (SIADH), and the reset osmostat syndrome.

In glucocorticoid deficiency, vasopressin secretion is incompletely suppressed, despite hypo-osmolality.2, 57, 75 Despite relative hypotension, the hyponatremia associated with pure glucocorticoid deficiency is asso-
ciated with low to normal renin levels and does not correct with saline infusion, indicating that hemodynamic factors do not underlie the disturbance. The persistent, nonosmotic release of vasopressin is thought to result from the loss of a tonic inhibition of vasopressin release by basal cortisol secretion. Glucocorticoid deficiency also has direct effects on renal blood flow and tubular function, which may contribute to the development of hyponatremia. Glucocorticoid replacement results in a prompt water diuresis and resolution of hyponatremia.

Severe hypothyroidism is also associated with nonosmotic vasopressin release and hyponatremia. The low cardiac output state associated with severe hypothyroidism decreases distal delivery of solute to the diluting segment and stimulates vasopressin release. The defect in water handling corrects with thyroid hormone replacement.

The usual cause of diuretic-associated hyponatremia is volume depletion. Thiazide diuretics, however, can occasionally cause severe euvoletic hyponatremia. This syndrome is more common in women than in men and can occur as soon as 1 day after starting the medication. The cause is multifactorial. Thiazide diuretics inhibit free water generation in the diluting segments of the nephron, restricting renal water excretion. In some patients, thiazides induce polydipsia, causing water ingestion to exceed the reduced capacity for excretion. In other patients, severe potassium depletion has been implicated as a cause.

Vasopressin levels in these patients are variable, with some studies showing undetectable vasopressin in the setting of hyponatremia and other studies demonstrating elevated vasopressin levels.

SIADH is characterized by an inappropriately concentrated urine (>100 mOsm/kg) in the setting of hypotonicity. The diagnosis is one of exclusion. Diagnostic criteria for SIADH are as follows:

1. Hypotonic hyponatremia.
2. Urine osmolality greater than 100 mmol/kg.
3. Absence of extracellular volume depletion.
4. Normal thyroid and adrenal function.
5. Normal cardiac, hepatic, and renal function.

There are a wide variety of causes (Table 1). In one study of hospitalized patients, the most common causes were postoperative state (30%), active intracranial disease (17%), cancer (17%), medications (9%), and pneumonia (5%). In some patients, an underlying cause cannot be identified on initial presentation; many of these patients are later found to have an underlying malignancy.

An important variant of SIADH is the rest osmostat syndrome. Patients with this disorder regulate their serum osmolality around a reduced set-point. In contrast to classic SIADH, they are able to dilute their urine normally in response to a water load and concentrate their urine in response to dehydration. The syndrome occurs most frequently in settings of malnutrition, such as tuberculosis or alcoholism. These patients are asymptomatic and do not require specific therapy. The hyponatremia generally improves after treatment of the underlying con-
Table 1. CAUSES OF SYNDROME OF INAPPROPRIATE SECRETION OF ANTIDIURETIC HORMONE

<table>
<thead>
<tr>
<th>Neoplasms</th>
<th>Pulmonary diseases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bronchogenic carcinoma</td>
<td>Tuberculosis</td>
</tr>
<tr>
<td>Pancreatic carcinoma</td>
<td>Pneumonia</td>
</tr>
<tr>
<td>Carcinoma of the duodenum</td>
<td>Bronchiectasis</td>
</tr>
<tr>
<td>Prostate carcinoma</td>
<td>Aspergillosis</td>
</tr>
<tr>
<td>Thymoma</td>
<td>Cystic fibrosis</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>Positive pressure ventilation</td>
</tr>
<tr>
<td>Mesothelioma</td>
<td>Medications</td>
</tr>
<tr>
<td>Central nervous system diseases</td>
<td></td>
</tr>
<tr>
<td>Head trauma</td>
<td></td>
</tr>
<tr>
<td>Subdural hematoma</td>
<td></td>
</tr>
<tr>
<td>Subarachnoid hemorrhage</td>
<td></td>
</tr>
<tr>
<td>Cerebrovascular accident</td>
<td></td>
</tr>
<tr>
<td>Meningitis</td>
<td></td>
</tr>
<tr>
<td>Encephalitis</td>
<td></td>
</tr>
<tr>
<td>Brain abscess</td>
<td></td>
</tr>
<tr>
<td>Hydrocephalus</td>
<td></td>
</tr>
<tr>
<td>Brain tumors</td>
<td></td>
</tr>
<tr>
<td>Guillain-Barré syndrome</td>
<td></td>
</tr>
<tr>
<td>Acute intermittent porphyria</td>
<td></td>
</tr>
<tr>
<td>Delirium tremens</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulmonary diseases</td>
<td></td>
</tr>
</tbody>
</table>

During pregnancy, there is physiologic resetting of the osmostat with plasma osmolality approximately 10 mmol/kg lower than in the nongravid state.

Clinical Approach to the Patient

The first step in the evaluation of hyponatremia is to confirm that hypotonicity is present by measuring the serum osmolality. If the osmolality is high, the presence of an osmotically active solute, such as glucose or mannitol, should be sought. If hypotonic hyponatremia is present, the evaluation should start with a physical examination focusing on volume status. Hypovolemia is suggested by orthostatic hypotension, tachycardia, dry mucous membranes, decreased central venous pressure, and poor skin turgor. Edema, ascites, increased central venous pressures, or rales heard on auscultation of the lungs suggest that congestive heart failure, cirrhosis, nephrotic syndrome, or renal insufficiency is an underlying cause.

In most cases, the urine is inappropriately concentrated (Fig. 3). A low urine osmolarity (<100 mmol/kg) suggests psychogenic polydipsia or advanced renal failure. Most patients with renal failure are able to dilute their urine; however, maximal free water excretion is reduced because of the decreased GFR.

It is frequently difficult to distinguish between volume depletion and euvoletic hyponatremia on clinical examination. In these situa-
Confirm Hypotonic Hyponatremia

Measure Uosm

Uosm < 150 mmol/kg

Appropriate Urinary Dilution

Psychogenic Polydipsia

Uosm > 150 mmol/kg

Assess Renal Function

Impaired Renal Function

Primary Renal Disease

Normal Renal Function

Assess Volume Status

Edema

Decreased Effective Arterial Volume

Volume-Mediated Vasopressin Secretion

Volume Depletion

Inappropriate Vasopressin Secretion

Euolemic

Assess Adrenal and Thyroid Function

Abnormal

Adrenal or Thyroid Insufficiency

Normal Function

Able to Dilute in Response to a Water Load

Yes

Reset Osmostat

No

SIADH

Figure 3. Diagnostic approach to hypotonic hyponatremia. Uosm = urine osmolality; SIADH = syndrome of inappropriate antidiuretic hormone.
tions, measurement of the urine sodium concentration can be helpful. A low urine sodium concentration suggests decreased effective arterial volume, whereas in SIADH, the urine sodium is usually greater than 30 mmol/L. In acute SIADH, the mild volume expansion induces a natriuresis. Once the patient has reached a new steady-state, urine sodium excretion reflects sodium intake and is not low unless the patient has a low salt intake. Because of the mild volume expansion, urate excretion is also increased in SIADH. A low serum uric acid level is therefore suggestive of SIADH, whereas volume depletion is associated with elevated levels. The diagnosis of SIADH also requires that adrenal and thyroid function be normal.

Treatment

The optimal treatment of hyponatremia is controversial. Some authors have stressed that untreated hyponatremia leads to permanent neurologic damage or death and needs to be treated rapidly, whereas others argue that rapid correction of hyponatremia can lead to central pontine myelinolysis and permanent neurologic dysfunction. The authors’ recommendations for treatment are based on the current understanding of the brain’s adaptation to hyponatremia. Acutely, in the setting of hyponatremia, there is cell swelling as water enters the intracellular compartment to maintain osmotic equilibrium. Adaptive processes are rapidly activated, which restore the brain volume toward normal. Initially, there is rapid loss of intracellular potassium. Although this reduces brain volume, it does not return it to normal, and the loss of electrolytes can impair membrane function and excitability. If hyponatremia persists, there is a loss of organic solutes (e.g., taurine, myoinositol, choline-containing compounds) over a period of hours to days, resulting in restoration of brain volume to normal and preservation of cell function.

The degree of brain swelling, and hence symptoms, depends on the rate of development, magnitude, and duration of the hypotonicity. Mild hyponatremia (sodium > 125 mmol/L) is usually asymptomatic. With more severe acute hyponatremia, nausea, headache, confusion, agitation, and incontinence may develop. Seizures, coma, respiratory arrest, and death can occur with profound acute hyponatremia. The symptoms associated with chronic hyponatremia are generally milder: lethargy, confusion, and malaise. Seizures are less common but may also occur. There is a poor correlation between the severity of symptoms and the degree of chronic hyponatremia, reflecting variable degrees of brain adaptation.

Central pontine myelinolysis (CPM) is a rare disorder characterized by spastic quadriplegia, pseudobulbar palsy, swallowing dysfunction, and mutism. On autopsy, there is demyelination in the central pons and extrapontine sites. Although CPM may occur in a number of clinical settings, it is associated with rapid correction of hyponatremia.
Initially, improvement of the neurologic symptoms associated with hyponatremia is observed, followed by the insidious development of the signs of CPM. The cause of CPM is not known, but the risk of its developing is related to the duration of hypotonicity (time for the brain to lose osmoles), the rate of its correction (to allow time to reacquire lost electrolytes and osmoles), and the overall magnitude of change of the plasma sodium concentration. The treatment of hyponatremia must therefore be individualized, taking into account its magnitude, duration, and associated symptoms as well as its cause. Hypotonicity associated with volume depletion is best treated by volume expansion with normal saline. Once the patient is euvoletic, the stimulus for vasopressin secretion is gone and there is prompt excretion of the retained water. Patients with hyponatremia secondary to nephrotic syndrome, heart failure, and cirrhosis should be treated with water restriction. In the case of heart failure, the hyponatremia may improve with the use of angiotensin converting enzyme inhibitors or other therapy to improve myocardial function. Loop diuretics may also be beneficial in edematous patients because they interfere with urine concentration and promote free water excretion. Patients with psychogenic polydipsia usually correct their hyponatremia spontaneously, if access to continued water ingestion is denied.

Asymptomatic or minimally symptomatic patients with euvoletic chronic hyponatremia are best managed conservatively with fluid restriction and discontinuation of any medications that interfere with free water excretion. To be effective, fluids need to be restricted to less than free water losses. In patients with maximal urinary concentration, fluid intake must be reduced to less than insensible losses to correct the hyponatremia. Symptomatic chronic hyponatremia requires more rapid correction. There is a general consensus that initial therapy of the symptomatic patient should raise serum sodium concentration by no more than 1 to 2 mmol/L/hour. As soon as clinical improvement has occurred, the rate of correction should be reduced, and the overall increase in the serum sodium concentration should be no more than 12 mmol/L over the first 24 hours. Similar treatment should be instituted for severe acute hyponatremia, even if only relatively minor symptoms are present, because more significant symptoms can emerge suddenly. When rapid correction of hyponatremia is required, hypertonic (3%) saline should be administered at a rate of 1 to 2 mL/kg/hour, with close monitoring of the serum sodium concentration. If volume overload occurs, a loop diuretic should be administered. Normal saline is not an appropriate treatment of SIADH; the sodium infused may be rapidly excreted while the water is retained, worsening the hyponatremia. In all cases, water restriction is an important adjunct. Most cases of SIADH are self-limited (e.g., pneumonia, postsurgical). If the hyponatremia is prolonged and the patient does not tolerate water restriction, demeclocycline may be of benefit. This tetracycline antibiotic, at a dose of 600 to 1200 mg/day, induces nephrogenic diabetes insipidus and is an important adjunct to fluid restriction in patients with chronic SIADH. Side effects of
demeclocycline include azotemia, photosensitivity, and nausea, and it is contraindicated in patients with liver disease or renal failure.31

HYPERNATREMIA

In contrast to hyponatremia, which usually results from a defect in renal water handling, the primary defect in hypernatremia is impaired water intake. Rises in serum osmolality induce intense thirst and stimulate water ingestion. Sustained hypertonicity implies a defect in thirst sensation or restricted access to water.39, 40 Patients with complete diabetes insipidus are polyuric (up to 20 L/day) but do not develop hypernatremia unless water intake is restricted. In rare cases, hypernatremia can result from the ingestion or administration of salt or hypertonic fluids; however, the hypernatremia is transient unless water intake is impaired.32, 37, 68, 74, 116

The incidence of hypernatremia in hospitalized patients ranges from 0.3% to 1%, with 60% to 80% developing hypernatremia following hospital admission.19, 64, 81, 104 The characteristics of patients who acquire hypernatremia in the hospital differ from those who are admitted with hypernatremia.81 The typical patient admitted with hypernatremia is an elderly, female nursing home resident.81, 104 Underlying infections are the most common admitting diagnosis.65, 81 In contrast, patients who acquire hypernatremia during the course of hospitalization do not differ in age from the general hospitalized population and are evenly split between men and women.81 It is important to realize that hypernatremia developing in the hospital is often iatrogenic, resulting from inadequate free water administration.81, 104 In a study of hospital-acquired hypernatremia, most of the patients who developed hypernatremia were intubated or had impaired mental status and could not regulate their water intake to compensate for increased water losses. The prescribed free water administration was inadequate.61 The mortality rate from hypernatremia is reported to be 40% to 55%, but as in the case of hyponatremia, the majority of deaths do not reflect the hypernatremia per se and are related to the underlying disease process.64, 81, 104 It does appear, however, that delayed or inappropriate treatment is associated with an increase in deaths attributable to the hypertonic state.81

Causes

Thirst provides the ultimate defense against hypernatremia. In the absence of thirst, hypernatremia may develop in the setting of usual insensible losses. In patients with primary hypodipsia, thirst is diminished or absent despite appropriate osmotic or hemodynamic stimuli.92 If the defect in water intake is mild and vasopressin secretion is maintained, renal water conservation may be adequate to prevent hypernatremia. With more severe defects, progressive hypernatremia occurs.
Primary hypodipsia results from destruction of the thirst centers in the hypothalamus. A wide variety of disorders have been implicated, including primary and metastatic (most commonly breast and lung) tumors of the hypothalamus (50%), granulomatous diseases (20%), vascular abnormalities (15%), and trauma. Lesions may involve only the thirst centers or may also involve the osmoreceptors for vasopressin secretion and result in both hypodipsia and diabetes insipidus. In a small number of cases, hypodipsic hypernatremia has been described in geriatric patients who do not manifest any hypothalamic pathology. An important variant of primary hypodipsia is the syndrome of essential hypernatremia, which represents the hypertonic counterpart of the reset osmostat. In this syndrome, there is an upward resetting of the osmotic thresholds for thirst and vasopressin release, although the response to hemodynamic stimuli is normal.

More commonly, hypernatremia results from inadequate fluid intake in the setting of increased free water losses. Geriatric patients are at increased risk because renal concentrating ability and thirst decline with age, although the osmoreceptors' response to hypernatremia is maintained. Water intake is also impaired in hospitalized patients because of debility, altered sensorium, sedation, or intubation. These patients are at increased risk for hypernatremia if care is not taken to prescribe adequate free water replacement. Increased free water losses may occur as pure water loss (fever, hyperventilation, diabetes insipidus) or the result of hypotonic fluid losses (burns, gastrointestinal losses, diuretic therapy, osmotic diuresis).

Diabetes insipidus results from deficient vasopressin secretion (hypothalamic) or end organ hyporesponsiveness to vasopressin (nephrogenic). Severe diabetes insipidus is characterized by marked polyuria with the excretion of a dilute urine and secondary polydipsia. Less severe forms of diabetes insipidus arise from partial defects and are associated with more moderate degrees of polyuria and an inability to concentrate the urine maximally. Hypothalamic diabetes insipidus results from damage to the neurons that synthesize and secrete vasopressin and is associated with multiple causes (Table 2). Nephrogenic diabetes insipidus can be congenital or acquired (Table 3). Congenital nephrogenic diabetes insipidus is a rare inherited disorder that is usually the result of mutation of the V2-receptor gene, although a few kindreds have been described in whom the defect is in the aquaporin-2 water channel. Acquired nephrogenic diabetes insipidus is most commonly caused by medications (notably lithium), although it may also result from obstructive uropathy, chronic tubulointerstitial diseases, hypercalcemia, or severe potassium depletion.

Patients with hypotonic losses develop both hypernatremia and volume depletion. The majority of gastrointestinal fluids are hypotonic. Prolonged nasogastric suction, vomiting, and diarrhea frequently contribute to the development of hypernatremia. Hypernatremia may also develop in the setting of third space losses (e.g., ileus, pancreatitis, bowel obstruction) if there is not adequate replacement of free water.
Table 2. CAUSES OF HYPOTHALAMIC DIABETES INSIPIDUS

<table>
<thead>
<tr>
<th>Causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Head trauma</td>
</tr>
<tr>
<td>Postsurgical (hypophysectomy)</td>
</tr>
<tr>
<td>Tumors</td>
</tr>
<tr>
<td>Craniorhynghroma</td>
</tr>
<tr>
<td>Pinealoma</td>
</tr>
<tr>
<td>Meningioma</td>
</tr>
<tr>
<td>Germinoma</td>
</tr>
<tr>
<td>Glioma</td>
</tr>
<tr>
<td>Benign cysts</td>
</tr>
<tr>
<td>Leukemia/lymphoma</td>
</tr>
<tr>
<td>Metastatic tumors</td>
</tr>
<tr>
<td>Infections</td>
</tr>
<tr>
<td>Tuberculosis</td>
</tr>
<tr>
<td>Syphilis</td>
</tr>
<tr>
<td>Mycoses</td>
</tr>
<tr>
<td>Toxoplasmosis</td>
</tr>
<tr>
<td>Encephalitis</td>
</tr>
<tr>
<td>Basilar meningitis</td>
</tr>
<tr>
<td>Granulomatous diseases</td>
</tr>
<tr>
<td>Sarcoidosis</td>
</tr>
<tr>
<td>Histiocytosis X/eosinophilic</td>
</tr>
<tr>
<td>granuloma</td>
</tr>
<tr>
<td>Wegener's granulomatosis</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
</tr>
<tr>
<td>Aneurysms</td>
</tr>
<tr>
<td>Cerebrovascular accident</td>
</tr>
<tr>
<td>Infections</td>
</tr>
<tr>
<td>Tuberculosis</td>
</tr>
<tr>
<td>Syphilis</td>
</tr>
<tr>
<td>Mycoses</td>
</tr>
<tr>
<td>Toxoplasmosis</td>
</tr>
<tr>
<td>Encephalitis</td>
</tr>
<tr>
<td>Basilar meningitis</td>
</tr>
</tbody>
</table>

Significant hypotonic fluid losses may occur through the skin in patients with severe burns and from perspiration during strenuous exercise. Renal hypotonic losses commonly result from diuretic administration or during osmotic diuresis from glucose, mannitol, or urea. A urea-induced osmotic diuresis may occur in the setting of protein overfeeding or extreme catabolism, as a result of the large filtered urea load created by protein breakdown. Renal salt wasting from tubulointerstitial diseases, mineralocorticoid deficiency, or postobstructive diuresis can also produce hypotonic losses.

Pure hypertonic solute gain, or the gain of solute in excess of water, produces hypertonicity and extracellular volume expansion. This may occur following the accidental ingestion of large quantities of salt or as the result of the administration of hypertonic saline or bicarbonate-containing solutions. Adult ingestion of salt is uncommon, but

Table 3. CAUSES OF NEPHROGENIC DIABETES INSIPIDUS

<table>
<thead>
<tr>
<th>Causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congenital</td>
</tr>
<tr>
<td>Vasopressin V2-receptor</td>
</tr>
<tr>
<td>mutations</td>
</tr>
<tr>
<td>Aquaporin-2 water channel</td>
</tr>
<tr>
<td>mutations</td>
</tr>
<tr>
<td>Medications</td>
</tr>
<tr>
<td>Lithium</td>
</tr>
<tr>
<td>Amphotericin B</td>
</tr>
<tr>
<td>Demeclocycline</td>
</tr>
<tr>
<td>Methoxyflurane</td>
</tr>
<tr>
<td>Obstructive uropathy</td>
</tr>
<tr>
<td>Chronic tubulointerstitial diseases</td>
</tr>
<tr>
<td>Analgesic abuse nephropathy</td>
</tr>
<tr>
<td>Sickle cell nephropathy</td>
</tr>
<tr>
<td>Multiple myeloma</td>
</tr>
<tr>
<td>Amyloidosis</td>
</tr>
<tr>
<td>Sarcoidosis</td>
</tr>
<tr>
<td>Sjögren's syndrome</td>
</tr>
<tr>
<td>Autoimmune/lupus</td>
</tr>
<tr>
<td>Polycystic kidney disease</td>
</tr>
<tr>
<td>Medullary cystic disease</td>
</tr>
<tr>
<td>Electrolyte disorders</td>
</tr>
<tr>
<td>Hypercalcemia</td>
</tr>
<tr>
<td>Potassium depletion</td>
</tr>
</tbody>
</table>
hypernatremia in infants has occurred when salt was inadvertently substituted for sugar in the preparation of formula or concentrated formulas were administered without diluting. The iatrogenic administration of hypertonic fluids can occur as the result of inappropriate sodium prescription in parenteral nutrition, from bicarbonate administration during cardiac arrest, or from the inadvertent intravenous administration of hypertonic saline during abortion. With normal thirst and renal function, increased water intake corrects the hypertonicity, and the excess sodium is rapidly excreted. Persistent hypernatremia therefore implies decreased water intake or renal impairment.

Diagnostic Approach

The signs and symptoms of hypernatremia are nonspecific and relate to cellular dehydration, especially in the brain. As a result of the extracellular hypertonicity, water leaves the intracellular compartment and cells shrink. In the brain, this can lead to traction on the dural veins and venous sinuses leading to intracranial hemorrhage. Common manifestations of hypernatremia include restlessness, irritability, lethargy, muscular twitching, hyperreflexia, and spasticity.

Patients with hypernatremia secondary to pure water loss often do not appear hypovolemic. The water is lost from all body compartments (intracellular and extracellular), and unless losses are extreme, they do not produce signs of volume depletion. In contrast, patients with hypotonic losses present with signs of hypovolemia, including tachycardia, orthostatic hypotension, decreased central venous pressure, and dry mucous membranes.

Urine osmolality and sodium concentration may be useful in the differential diagnosis of hypernatremia. Extrarenal hypotonic losses are associated with a low urine sodium and a maximally concentrated urine (>700 mmol/kg). When losses are renal in origin, the urine osmolality is inappropriately low. With diuretics, osmotic diuresis, or salt wasting, the urine tends to be isotonic (urine osmolality approximately 300 mmol/kg).

A urine osmolality less than 150 mmol/L in the setting of hypertonicity and polyuria is diagnostic of diabetes insipidus. Formal dehydration testing is rarely required and may be hazardous in patients with severe diabetes insipidus, but it is useful in the diagnosis of partial defects. The hypothalamic and nephrogenic forms can usually be differentiated on the basis of the change in urine osmolality following exogenous vasopressin or by the measurement of circulating vasopressin levels following dehydration testing.

Treatment

As with hyponatremia, chronic hypernatremia is tolerated better than the acute disturbance, although the mortality is high in both states.
In chronic hypernatremia, there has been time for brain adaptation. Hypertonicity leads to cell shrinkage. The initial response of the brain is to alter ion transport and accumulate intracellular electrolytes. Although this increases cell volume toward normal, it can impair cell function. With chronic hypernatremia, there is accumulation of organic solutes (amino acids, trimethylamines, myoinositol). Although this adaptation ameliorates the symptoms of hypertonicity, it puts the patient at risk for cerebral edema if the hypernatremia is corrected too quickly.

The treatment of hypernatremia is water administration. Existing water deficits and continuing water losses must be replaced. The water deficit can be calculated as:

$$\text{Free water deficit} = 0.6 \times \text{body weight (kg)} \times \left(\frac{\text{plasma sodium}}{140} - 1\right)$$

Although this formula is based on many assumptions, it provides a useful first approximation for initiating water replacement.

Water can be replaced enterally (oral or via nasogastric tube) as pure water, or it can be replaced intravenously with hypotonic saline or 5% dextrose in water. When using glucose-containing solutions, the glucose levels should be monitored because hyperglycemia worsens the hyperosmolarity and can lead to an osmotic diuresis. In addition to replacing the calculated water deficit, ongoing fluid losses must also be replaced. If possible, the cause of the increased losses should be addressed.

In acute hypernatremia, the water deficit can be replaced relatively rapidly. In chronic hypernatremia (>24 to 48 hours' duration), plasma sodium should be decreased by 1 to 2 mmol/L/hour until symptoms resolve and then the rate of correction slowed so that the sodium is normalized over the ensuing 24 to 48 hours. Deterioration in neurologic symptoms after initial improvement suggests the development of cerebral edema and requires temporary discontinuation of water replacement. In patients with volume depletion, therapy should aim first at restoring intravascular volume and then at correcting the water deficit. In patients with hypernatremia secondary to solute administration, the hypernatremia is acute and can be rapidly corrected. These patients usually are volume overloaded and require both water administration and solute removal. A loop diuretic can be administered along with water to facilitate sodium excretion. In patients with massive volume overload or renal failure, dialysis may be necessary.

Once hypernatremia is corrected, patients with primary hypodipsia should be treated by prescribing daily fluid intake as a medication order. The prescription can be adjusted for periods of increased water loss (such as fever or exercise). Patients with diabetes insipidus and intact thirst drink enough fluids to prevent hypernatremia, although at the expense of significant polyuria. Treatment is designed to reduce urine output and reduce water intake to tolerable levels. Hypothalamic diabetes insipidus is treated with hormone replacement. This can be accomplished using aqueous vasopressin. DDAVP (1-deamino-(8-D-argi-
nine)-vasopressin), a synthetic analogue, however, has a longer half-life and has less vasoconstrictive effects than native vasopressin. The usual dose is 1 to 2 µg every 12 to 24 hours administered intravenously or subcutaneously or 5 to 20 µg every 12 hours given intranasally. Patients with partial diabetes insipidus often do not require hormone therapy. Chlorpropamide, which potentiates the renal effects of vasopressin, and carbamazepine, which enhances vasopressin secretion, have been used to treat partial hypothalamic diabetes insipidus but are associated with significant side effects.

In nephrogenic diabetes insipidus, hormone replacement is ineffective. Reducing solute delivery to the diluting segment limits free water generation and mitigates the polyuria. This can be accomplished by prescribing a low-salt diet combined with a thiazide diuretic to induce mild negative sodium balance. The addition of indomethacin may also be beneficial in reducing distal solute delivery. Where possible, medications causing nephrogenic diabetes insipidus should be discontinued. For lithium-induced nephrogenic diabetes insipidus, amiloride has proven to be particularly effective. Amiloride functions by blocking the sodium channel in the collecting duct epithelia, reducing lithium entry into the cells and decreasing its cellular toxicity. In addition, thiazide diuretics should be avoided in patients on long-term lithium because the negative sodium balance induced by thiazides increases proximal reabsorption of lithium (the major site of reabsorption of lithium) and can lead to lithium toxicity.

**SUMMARY**

Hyponatremia and hypernatremia are common electrolyte disorders resulting from disorders in water homeostasis. Hyponatremia usually results from defects in free water excretion, although increased intake may also contribute. The treatment of hyponatremia has been controversial because of the high associated morbidity and mortality and the observation that rapid correction of hyponatremia is associated with the development of central pontine myelinolysis. Mild hyponatremia should be treated with water restriction alone, whereas severe acute or symptomatic hyponatremia should initially be corrected rapidly until symptoms resolve followed by more gradual correction. In all cases, treatment should be individualized on the basis of severity, cause, and duration of the hyponatremia.

Hypernatremia results from impaired water ingestion, although increased water losses are often contributory. Hospital-acquired hypernatremia is usually iatrogenic because of inadequate water prescription and is therefore preventable. Hypernatremia is also associated with high morbidity and mortality, both as a result of the underlying disease and inadequate treatment. The primary treatment of hypernatremia is water replacement—repleting water deficits and replacing ongoing losses. Additional treatment should be directed at eliminating excess water losses.
References

27. DeFronzo RA, Goldberg M, Agus ZS: Normal diluting capacity in hyponatremia
patients: Reset osmostat or a variant of the syndrome of inappropriate antidiuretic hormone secretion. Ann Intern Med 84:538, 1976
71. Miller JH, Shock NW: Age differences in the renal tubular response to antidiuretic hormone. J Gerontol 8:446, 1953
FRIED & PALEVSKY


109. Teitelbaum I, Kleeman CR, Berl T: The physiology of the renal concentrating and

Address reprint requests to
Paul M. Palevsky, MD
Renal-Electrolyte Division
A919 Scaife Hall
3550 Terrace Street
Pittsburgh, PA 15213