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Hyponatremia and hypernatremia

A systematic approach to causes and their correction

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CME learning objectives

- To learn an approach to patient evaluation for hyponatremia and hypernatremia
- To identify patients at risk of complications from hyponatremia and hypernatremia
- To understand how to safely and effectively treat hyponatremia and hypernatremia

This page is best viewed with a browser that supports tables

Preview: Disorders of sodium and water metabolism are common in hospitalized patients and are occasionally encountered in outpatients. Both hyponatremia and hypernatremia can cause substantial morbidity and mortality, and ironically, incorrect treatment can add to the problem. In this article, Dr Fall outlines a general approach to evaluation and management of both conditions, with recommendations on safe and effective therapy.
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Osmotic forces determine the distribution of water between body fluid compartments. Each compartment has one major solute. Sodium is primarily extracellular, whereas potassium is primarily intracellular (1). In general, cell membranes (except for the renal medulla) are freely permeable to water. Therefore, water moves across a cell membrane until osmotic pressure is equal in the two compartments. This property allows brain cells to swell in the face of hyponatremia or shrink with hypernatremia, and

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it is responsible for the neurologic manifestations of acute sodium disorders.

The osmolality of a solution is defined by the number of solute particles per kilogram of water. The extracellular osmoles consist primarily of sodium salts, glucose, and urea. Serum osmolality is defined by the following equation:

Serum osmolality = (2 X Na) + (glucose ÷ 18) + (urea ÷ 2.8)

Under normal conditions, glucose and urea contribute minimally to serum osmolality. Osmolality is determined primarily by the serum sodium concentration. Serum osmolality is tightly regulated between 275 and 290 mOsm/kg, primarily through the influence of antidiuretic hormone (ADH). Osmoreceptors in the hypothalamus detect serum osmolality changes as small as 1%. An increase in serum osmolality or a decrease in the effective circulating volume can enhance the thirst mechanism. Likewise, water excretion is controlled by ADH, and an increase in serum osmolality or a decrease in circulating volume can stimulate ADH release. These changes in water intake and excretion maintain serum osmolality within the normal range.

Hyponatremia

Hyponatremia reflects an abnormal ratio of sodium to water and is defined as a serum sodium concentration of less than 135 mEq/L. It usually results from retention of water secondary to impairment in free water excretion. Occasionally, hyponatremia is due to sodium loss exceeding that of water (eg, thiazide-induced hyponatremia). Elderly women may be susceptible to this condition (2).

Excretion of free water has two general requirements: (1) generation of free water and dilute urine by reabsorption of sodium chloride without water in the ascending limb of the loop of Henle, and (2) excretion of this water by maintenance of impermeability to water (no ADH) in the collecting duct. ADH release is maximally suppressed at a serum osmolality of 275 mOsm/kg, as depicted in figure 1 (not shown) (3).

Because the capacity to excrete water is so great, water retention leading to hyponatremia occurs only when there is a defect in renal water excretion or when the system is overwhelmed (eg, in primary polydipsia). The normal daily osmolar load is about 10 mOsm/kg of body weight, and urine can be diluted as low as 50 mOsm/kg. Consequently, a 70-kg (154-lb) person can excrete up to 14 L (14.8 qt) of urine daily.

Clinical features

Signs and symptoms of hyponatremia are primarily related to the central nervous system. In hyponatremia, the osmotic pressure gradient favors movement of water into brain cells, resulting in cerebral edema. The brain has adaptive capabilities that serve to minimize cell swelling, but in patients with acute development of hyponatremia, this adaptation cannot occur (4).

Early manifestations of hyponatremia include anorexia,

nausea, lethargy, and apathy. More advanced symptoms include disorientation, agitation, seizures, depressed reflexes, focal neurologic deficits and, eventually, Cheyne-Stokes respiration (5). Coma and seizures usually occur only with acute reduction of the serum sodium concentration to less than 120 mEq/L (6).

Hence, clinical manifestations of hyponatremia correlate with the serum sodium concentration and, more important, with how rapidly the condition developed. The mortality rate of hyponatremia has been cited as ranging from 5% to 50%, depending on severity and acuity of onset (7).

Diagnosis

The diagnostic process in hyponatremia involves performing thorough history taking and physical examination and obtaining three basic laboratory values: serum osmolality, urine osmolality, and urine sodium (5). This information is used to determine the cause of hyponatremia and help guide therapy. Common causes of hyponatremia include the syndrome of inappropriate ADH and depletion of effective circulating volume.

Important information to obtain in history taking includes use of medications (particularly thiazide diuretics), recent vomiting, diarrhea or excessive sweating with hypotonic fluid ingestion, recent surgery, and a history of psychiatric illness, congestive heart failure (CHF), cirrhosis, or nephrotic syndrome with renal failure. Physical examination should focus on assessment of volume status and include orthostatic vital signs, skin turgor, mucous membrane appearance, jugular venous distention, findings of edema, and wedge pressure and central venous pressure if available.

The initial laboratory measurement needed in evaluation of hyponatremia is serum osmolality. A common cause of hyperosmolar hyponatremia (ie, serum osmolality >290 mOsm/kg) is hyperglycemia; hypertonic infusion of mannitol (Osmitrol) is a less common cause. Isosmolar hyponatremia (ie, normal serum osmolality of 275 to 290 mOsm/kg) may, rarely, be caused by pseudohyponatremia from either severe hyperlipidemia or hyperproteinemia. The finding results from the method used to measure the serum sodium concentration and does not represent true hyponatremia. Hypo-osmolar hyponatremia (ie, serum osmolality <275 mOsm/kg) is the most common type. Causes are listed in table 1 and are the focus of the remaining discussion.

Table 1. Differential diagnosis of hypo-osmolar hyponatremia

Volume status and condition	Urine sodium concentration (mEq/L)
Hypovolemic	
Renal loss (through diuretic use, salt-wasting nephropathy, hypoaldosteronism)	>20
Gastrointestinal loss (through vomiting, diarrhea, tube drainage)	<10

Skin loss (through sweating, burns, cystic fibrosis)	<10
Peritonitis	<10
Euvolemic	
Antidiuretic hormone (ADH) excess (through syndrome of inappropriate ADH, use of thiazide diuretics or oral hypoglycemic agents)	>30
Pain	>30
Postoperative state (including transurethral prostatic resection syndrome)	>30
Cortisol deficiency	>30
Hypothyroidism	>30
Decreased solute intake	Variable
Psychogenic polydipsia	Variable
Resetting of osmostat (pregnancy, psychiatric disorders)	Variable
Hypervolemic	
Congestive heart failure	<10
Cirrhosis	<10
Nephrotic syndrome	<10
Acute and chronic renal failure	>20

The next measurement needed in evaluation of hyponatremia is urine osmolality. This value indicates whether water excretion is impaired. Normally, when the body is faced with a water load, serum osmolality is decreased, ADH is suppressed, and excess free water is excreted in very dilute urine (osmolality as low as 50 mOsm/kg). Patients with hyponatremia and urine osmolality of less than 100 mOsm/kg are appropriately excreting very dilute urine, as occurs in primary polydipsia and resetting of the osmostat (ie, a form of the syndrome of inappropriate ADH in which serum osmolality is reset downward to a new threshold). In patients with resetting of the osmostat, a serum sodium concentration between 125 and 130 mEq/L is usually maintained, with appropriate excretion of dilute urine during water loading. However, most patients with hyponatremia have urine osmolality of more than 200 mOsm/kg, reflecting impairment in water excretion.

The final step in evaluation of hyponatremia is to measure the urine sodium concentration and use this finding in conjunction with volume status to determine the cause of hyponatremia and help guide therapy. In general, a spot test showing urine sodium concentration of less than 30 mEq/L differentiates patients with hypovolemic hyponatremia from patients with euvolemic hyponatremia (who have urine sodium concentration greater than 30 mEq/L on spot testing) (table 1) (8). (Spot testing of urine

sodium concentration can also be helpful in identifying hypervolemic hyponatremia.)

In interpreting urine sodium concentration, the following caveats should be considered: A high urine sodium concentration may be found in patients with volume depletion secondary to a renal cause of salt wasting (eg, adrenal insufficiency, thiazidediuretic use), metabolic alkalosis, or osmotic diuresis (eg, from hyperglycemia). The so-called sodium-avid states of CHF, cirrhosis, and nephrotic syndrome all typically have a low urine sodium concentration unless patients are taking a diuretic, whereas renal failure tends to cause a high urine sodium concentration (table 1).

Treatment

Much has been written about treatment of hyponatremia and the potential adverse outcome of central pontine myelinolysis (9,10). This condition is demyelination of the pons, which can lead to mutism, dysphasia, spastic quadriparesis, pseudobulbar palsy, delirium, coma, and even death.

On the basis of observations in both animals and humans, it appears that aggressive treatment of hyponatremia that has been present for longer than 24 to 48 hours is responsible for development of central pontine myelinolysis. Raising the serum sodium concentration more than 25 mEq/L or to a normal or above-normal level in the first 48 hours increases the likelihood of central pontine myelinolysis. In addition, certain patients have a greater propensity for the disorder (eg, alcoholics, elderly women taking thiazide diuretics, patients who are malnourished or hypokalemic, burn patients) (11).

Treatment of hyponatremia varies depending on whether symptoms are present (11-14).

In asymptomatic patients: When symptoms are absent, the focus of therapy should be on identifying and correcting the underlying cause of hyponatremia. If a patient is judged to be hypovolemic on the basis of clinical assessment and urine sodium concentration, normal saline solution should be administered initially to correct the extracellular fluid volume deficit. If a patient is hypervolemic, salt and water restriction is key.

Most patients with CHF or nephrotic syndrome maintain a serum sodium concentration of more than 125 mEq/L, even with marked increase in ADH levels. Patients with CHF can be treated with inotropes, afterload reduction, and loop diuretics in addition to salt and water restriction. Loop diuretics are the mainstay of therapy in patients with nephrotic syndrome, and if these agents are unsuccessful, dialysis may be warranted.

For patients who are euvolemic and hyponatremic, therapy consists primarily of water restriction. Again, treating the underlying cause is important (eg, withdrawing a thiazide diuretic, initiating hormone therapy for hypothyroidism or adrenal insufficiency) and may correct the hyponatremia. When the cause of the syndrome of inappropriate ADH is unknown or not treatable, other methods can be used, including increased dietary protein and salt and use of urea, loop diuretics and, rarely, demeclocycline hydrochloride

(Declomycin).

In symptomatic patients: Patients with acute symptomatic hyponatremia are candidates for aggressive treatment (11,14). In this condition, acute hyponatremia develops so quickly (within 48 hours) that the brain has little time for adaptation. It most commonly occurs in hospitalized patients who receive hypotonic fluids postoperatively. Young menstruating women seem to be particularly susceptible to hyponatremic encephalopathy (15).

Hyponatremia can be corrected with administration of hypertonic saline solution (3%) at a rate of about 1 mL/kg per hour. A loop diuretic may be added to enhance water excretion if urine osmolality is greater than 300 mOsm/kg. With use of this combination therapy, sodium lost in the urine is replaced with an equal amount of sodium in a smaller volume. The serum sodium concentration should be raised no more than 25 mEq/L in the first 48 hours, at a rate of no more than 2 mEq/L per hour, and the target goal should be 120 to 125 mEq/L. Treatment with hypertonic saline solution is advocated only for patients with severe hyponatremia who have profound neurologic symptoms.

The main controversy in the literature surrounds treatment of chronic symptomatic hyponatremia because, as mentioned, central pontine myelinolysis may result if the condition is corrected too rapidly (11,14). Therefore, although treatment in these patients is similar to that just described, the rate of correction should be slower (0.5 to 1 mEq/L per hour). Aggressive therapy should be discontinued when the serum sodium concentration is raised 10% or symptoms abate.

Regardless of whether a symptomatic patient presents with acute or chronic hyponatremia, the key to successful management is frequent monitoring of serum electrolytes to ensure adherence to the guidelines outlined. In general, the serum sodium concentration should be reassessed every 2 to 4 hours during active intervention.

Hypernatremia

Hypernatremia, like hyponatremia, reflects an abnormal ratio of sodium and water. It is defined as a serum sodium concentration exceeding 145 mEq/L. Unlike hyponatremia, hypernatremia always represents a hyperosmolar state. Hypernatremia results from water loss or sodium retention, although sodium retention occurs in only a few circumstances (eg, administration of hypertonic sodium bicarbonate during cardiopulmonary resuscitation). Thus, the underlying cause of hypernatremia in the vast majority of patients is water loss in excess of solute (table 2) (1).

Table 2. Differential diagnosis of hypernatremia

Volume status and condition	Urine sodium concentration (mEq/L)
Hypovolemic	
Renal losses (osmotic diuresis by	>20

means of glucose, urea, mannitol [Osmitrol] use)	
Insensible losses (through sweating, fever, respiration)	<10
Gastrointestinal losses (through diarrhea)	<10

Euvolemic	
Renal losses (through diabetes inspidus--nephrogenic or central)	Variable
Hypothalamic disorder (primary hypodipsia, resetting of osmostat)	Variable

Hypervolemic	
Hypertonic saline administration	>20
Sodium bicarbonate administration	>20
Primary hyperaldosteronism	>20

The two defense mechanisms against hypernatremia are stimulation of ADH release (resulting in maximal urinary concentration) and thirst (16). Release of ADH occurs at a slightly lower serum osmolality than does stimulation of thirst, but thirst is the main defense mechanism against hypernatremia. Hypernatremia is almost never found in an alert patient who has access to water and a normal thirst mechanism. In adults, hypernatremia is more common after age 60, primarily because increased age is associated with decreased osmotic stimulation of thirst and decreased maximal urinary concentration.

Concentration of urine requires two basic conditions: (1) a hypertonic medullary interstitium, and (2) osmotic equilibrium of urine in the collecting duct that has the hypertonic interstitium (requiring ADH). Central diabetes insipidus occurs when secretion of ADH is impaired through disruption of the hypothalamic nuclei, osmoreceptors, or supraopticohypophysial tract. The most common causes of central diabetes insipidus are head trauma, hypoxic or ischemic encephalopathy, and idiopathic conditions.

Nephrogenic diabetes insipidus can occur if the countercurrent mechanism in the kidney is disrupted or the ability to respond to ADH is impaired. Lithium use, hypercalcemia, hypokalemia, osmotic diuresis, and sickle cell anemia are common causes of nephrogenic diabetes insipidus.

Clinical features

As in hyponatremia, signs and symptoms of hypernatremia are primarily related to the central nervous system. In hypernatremia, the osmotic pressure gradient favors movement of water out of brain cells and leads to a decrease in brain volume. Neurologic manifestations (eg, lethargy, weakness, irritability, hyperreflexia, seizures, coma, and even death) are the result. The mortality rate ranges from 16% to 60%, depending on the patient

population examined (17).

Patients with diabetes insipidus usually do not present with neurologic symptoms because of the powerful thirst mechanism, which protects them from hypernatremia. Instead, these patients complain of polydipsia, polyuria, and nocturia.

Diagnosis

Important information to obtain during history taking includes evidence of recent fluid losses (including insensible losses from fever, sweating, or recent respiratory infection), alteration in mental status, and thirst (if the patient is alert). Assessing the patient's volume status and measuring urine osmolality and urine sodium concentration (table 2) can be helpful in establishing the cause of hypernatremia and in guiding therapy.

As shown in the equation on page 75, serum osmolality is always greater than 290 mOsm/kg in hypernatremia, representing a hyperosmolar state. Patients should have maximally concentrated urine and urine osmolality of greater than 800 mOsm/kg if defense mechanisms are intact and the renal concentrating mechanism is normal. A normal response is seen in patients with salt overload, insensible or gastrointestinal water losses, or primary hypodipsia.

Patients with urine osmolality of less than 200 mOsm/kg usually have some form of diabetes insipidus and can be differentiated by their response to exogenous ADH (18). However, most patients have urine osmolality between 200 and 800 mOsm/kg, which can reflect volume depletion in central diabetes insipidus, partial diabetes insipidus, or osmotic diuresis.

Treatment

Treatment of hypernatremia follows the same general principles as that of hyponatremia (19,20). Rapid correction should be avoided because of the brain's adaptive response to hypernatremia and the potential risk of cerebral edema. The current recommendation is to lower the serum sodium concentration by about 0.5 mEq/L per hour and to replace no more than half the water deficit in the first 24 hours. The following formula can be used to calculate the water deficit (total body water, in kilograms, is 60% of lean body mass in men and 50% in women):

Water deficit = total body water (serum sodium concentration ÷ 140 - 1)

In patients with hypovolemic hypernatremia, normal saline solution is indicated initially to correct the intravascular volume deficit. When that is accomplished, more hypotonic fluids (eg, 50% normal saline) can be used. In patients with hypervolemic hypernatremia, removing the source of salt excess, administering diuretics, and replacing water are important to successful therapy. Patients with euvolemic hypernatremia usually require water replacement alone--either free water orally or an infusion of 5% dextrose in water.

Again, frequent monitoring of electrolytes is key to successful management.

Summary

Disorders of sodium and water metabolism can be approached by following a few basic steps: Thorough history taking and physical examination that focuses on volume assessment and laboratory evaluation that includes serum osmolality, urine osmolality, and urine sodium concentration are usually all that are required for diagnosis. Results of these findings are helpful in guiding therapy. Monitoring serum sodium concentration often to ensure adequate treatment and to avoid potential complications is required in management of both hyponatremia and hypernatremia.

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