Hyponatremia:

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By Arielle Levitan, MD [1] and Gregory W. Rutecki, MD [2]

ABSTRACT: To identify the cause of hyponatremia, determine the patient's volume status and measure urinary sodium and osmolality; also ask about diuretic use. Hypovolemic hyponatremia is associated with vomiting, diarrhea, laxative abuse, renal disease, nasogastric suction, salt-wasting nephropathy, Addison disease, solute diuresis, and diuretic use. Euvolemic hyponatremia with a normal urinary sodium level can result from glucocorticoid deficiency, hypothyroidism, certain drugs, and the syndrome of inappropriate antidiuretic hormone secretion. Euvolemic hyponatremia with low urinary osmolality can be caused by psychogenic polydipsia, "tea and toast" syndrome, or beer potomania. Hypervolemic hyponatremia is associated with congestive heart failure, nephrotic syndrome, and cirrhosis. To reduce the risk of serious neurologic sequelae, avoid both undertreatment and overtreatment of hyponatremia. In chronic hyponatremia, total correction should not exceed 8 to 12 mEq/L/24 h (a maximum correction rate of 0.5 mEq/L/h). In acute hyponatremia, rates of correction up to approximately 1 mEq/L/h are acceptable. Avoid overcorrection of serum sodium concentration (ie, to a level higher than 140 to 145 mEq/L).

An understanding of hyponatremia and its treatment is critical to primary care practice. Both undertreatment and overtreatment of this common electrolyte disorder have been associated with irreversible neurologic complications and death. Here we present a step-by-step approach to the diagnosis of hyponatremia and an evidence-based treatment plan. On page 871, we offer treatment caveats and pearls for special patient populations, including women, patients who have recently undergone surgery, and marathon runners.

PATHOPHYSIOLOGY OF HYPONATREMIA
Because water can move freely across all cell membranes, any temporary osmotic gradient between the extracellular and intracellular compartments is rapidly brought into equilibrium. In patients with hyponatremia, water enters the body and both the intracellular and extracellular solute concentrations decrease. This produces a net increase in the water in brain cells-and thus swelling. A 10% change in brain water volume-either an increase or a decrease-can be fatal. However, the brain has 2 major defense mechanisms to mitigate the effects of water shifts:

The initial acute mechanism begins as soon as the water content of the brain changes. The subacute, or chronic, mechanism is completely effective approximately 48 hours after the initial change in brain water content is detected.

Acute adjustment. When brain water content increases (as in hyponatremia), excess fluid rapidly moves out of the CNS as a result of alterations in interstitial and cerebrospinal fluid flow. The increased movement of interstitial water out of brain cells and into the cerebrospinal fluid mitigates the initial brain swelling.

Chronic adjustment. If free water continues to increase, the second mechanism is activated: the rapid loss of intracellular electrolytes (sodium, potassium) as well as later losses of so-called organic osmolytes produces further adjustments in fluid flow. Organic osmolytes are divided into 3 classes: polyols (eg, sorbitol); amino acids (eg, taurine, alanine); and methylamines (eg, betaine). The concentration of these solutes can be up- or down-regulated by brain cells, and they play key roles in cell volume regulation.

In patients with hyponatremia, the brain reduces intracellular water uptake by actively decreasing intracellular osmolality (through down-regulation of electrolyte and organic osmolyte concentrations). This further mitigates increases in cell volume and actual brain swelling.

When defense mechanisms are insufficient or complicate treatment. The acute compensatory mechanism can be overcome by rapid, massive water gains. The initial defense mechanism is overwhelmed when water uptake exceeds 0.5 mEq/L/h or when sodium concentration quickly falls to 120 mEq/L or lower. When acute compensation is overcome, fatal levels of cerebral
edema can result. Because of the potential for excessive volume change, acute hyponatremia can have devastating consequences. Furthermore, the down-regulation of electrolyte and organic osmolyte levels that constitutes chronic adjustment complicates the correction of hyponatremia and can result in iatrogenic injury. For example, the administration of hypertonic saline to a patient with hyponatremia can shrink CNS cells with a down-regulated osmolyte level.

**UNMASKING THE CAUSE OF HYPONATREMIA**

The cause of hyponatremia has significant implications for management. Thus, the optimal workup focuses on the history and physical findings. These findings can be used to categorize hyponatremia as hypovolemic, euvolemic, or hypervolemic. Measurements of urinary sodium and osmolality from a random urine sample can help identify the cause of the water excess (Algorithm I).

Always inquire about diuretic use. Studies have clearly documented the serious risk of hyponatremic CNS complications attributable solely to diuretics. The thiazides and metolazone are typically responsible for the induction of hyponatremia; loop diuretics rarely produce hyponatremia. Here we will consider only the causes of hypotonic hyponatremia, since the majority of clinical cases fall into this category. In "Hyponatremia: Treatment Caveats and Pearls" (page 871), we discuss an important type of hypertonic hyponatremia-post- transurethral prostatectomy and posthysteroscopy syndromes.

**Hypovolemic hyponatremia.** The usual response of the kidneys to volume depletion is to conserve sodium and water-whether or not hyponatremia is present. Thus, it is useful to categorize patients with hypovolemic hyponatremia on the basis of their urinary sodium excretion pattern. Those whose kidneys are responding normally to their condition will have a low urinary sodium level (less than 20 mEq/L). Patients in this category are typically volume-depleted (for example, as a result of nasogastric aspiration) and are being replenished with hypotonic fluids (eg, 0.9% normal saline). A high urinary sodium level (greater than 20 mEq/L) can be a clue to the presence of diuretic use, underlying renal disease (including salt-wasting nephropathy), or Addison disease.

**Euvolemic hyponatremia.** A number of conditions are associated with euvolemic hyponatremia and a normal urinary sodium level and osmolality. The syndrome of inappropriate antidiuretic hormone secretion (SIADH) is a common cause of euvolemic hyponatremia, but it should be a diagnosis of exclusion. First, consider the endocrine disorders glucocorticoid deficiency and hypothyroidism. To miss a treatable endocrine disease could be a fatal mistake. In addition, if volume contraction is suspected, rule out Addison disease.

Glucocorticoid deficiency can result from an overly rapid taper of a corticosteroid regimen. In contrast to Addison disease, mineralocorticoid secretion remains intact in this setting. Certain drugs can also cause euvolemic hyponatremia. Cyclophosphamide, for example, can lead to hypotonicity. NSAIDs can cause vasoconstriction in the kidney and thereby reduce the excretion of water; however, this effect of NSAIDs is only seen in patients under stress. After other conditions have been ruled out, SIADH is the most likely diagnosis in a patient with euvolemic hyponatremia and a urinary sodium level greater than 20 mEq/L. In addition to the "typical" markers (euvolemic, urinary osmolality greater than that of plasma and, usually, a mild natriuresis), hypouricemia and hypouremia (signaled by low blood urea nitrogen and creatinine levels) are frequently seen. Follow any patient with SIADH closely, even if workup results are negative; some tumors that cause SIADH are diagnosed 6 to 12 months after the initial episode. Neoplasms associated with SIADH include lymphomas and bronchogenic, pancreatic, and ureteral cancers.

Three conditions are associated with euvolemic hyponatremia and decreased water clearance caused by low or inadequate solute intake and excessive water intake:

- "Tea and toast" syndrome.
- Beer potomania.
- Psychogenic polydipsia.

All 3 are characterized by substantial degrees of urinary hypoosmolality, which is unusual in hyponatremia. In fact, urinary osmolality can reach the point of maximal dilution (60 mOsm/kg of water) in any of these conditions; moreover, euvolemic hyponatremia with maximally dilute urine is seen only in patients with one of these conditions. Because urine must contain a certain amount of solute, the amount of free water that can be excreted by the kidneys is limited by the amount of solute ingested. Patients whose diet contains an inadequate amount of solute (as in "tea and toast" syndrome) and those who consume large quantities of beer (as in beer potomania) or excessive amounts of water (as in psychogenic polydipsia) do not have sufficient available solute to excrete all of their excess free water. Hyponatremia develops as a result.
Hypervolemic hyponatremia. The hallmarks of this disorder are ineffective circulation and the resultant retention of water and volume (the kidneys respond to ineffective circulating volume by retaining sodium and water). This generally leads to low urinary sodium levels and increased urinary osmolality-findings similar to those seen in patients with hypovolemic hyponatremia. If a patient with hypervolemic hyponatremia has a urinary sodium level of less than 20 mEq/L, consider a diagnosis of congestive heart failure (CHF), nephrotic syndrome, or liver disease. However, in some patients, the urinary sodium level is increased (greater than 20 mEq/L). One of the foregoing 3 conditions is usually present in such patients but is complicated by additional renal insufficiency or diuretic use.

CORRECTION OF HYponATREMIA

A formula for calculating the most efficient correction of hyponatremia is provided in the Box. Although considerable controversy surrounds the correction of both acute and chronic hyponatremia, the following guidelines are generally agreed on:

In chronic hyponatremia, total correction should not exceed 8 to 12 mEq/L/24 h (a maximum correction rate of 0.5 mEq/L/h). Despite this, rates up to approximately 1 mEq/L/h are acceptable. In fact, a rapid 5% increase in serum sodium concentration can reduce cerebral edema immediately. Signs or symptoms of severe acute or chronic hyponatremia (eg, seizures) will respond to a rapid 3 to 7 mEq/L rise in sodium concentration. However, do not exceed a total increase of 8 to 12 mEq/L/24 h.

Avoid overcorrection of serum sodium concentration (ie, to a level higher than 140 to 145 mEq/L). In patients with euvoletic or hypervolemic hyponatremia (eg, those in whom hyponatremia is associated with CHF or nephrotic syndrome), the use of furosemide during saline administration is beneficial. Loop diuretics lower urinary osmolality, which results in a more rapid rise in sodium concentration. However, frequent measurement of serum sodium concentration (every 2 to 4 hours, at least initially) is necessary to prevent either overly rapid correction (more than 0.5 mEq/L/h) or overcorrection.

Another technique for the prevention of overly rapid correction, particularly in patients who are hypervolemic, is to measure the amount of sodium lost in the urine and then replace only the amount lost with hypertonic saline. For example, if administration of 40 mg of furosemide leads to the excretion of 150 mEq of sodium over 2 hours in a patient with CHF (serum sodium level, 120 mEq/L), the 150 mEq of sodium can be replaced-without adding to the volume excess-by giving 3% or 5% saline solution.

Correct hypokalemia while hyponatremia is being treated.

Treat symptomatic hyponatremia-chronic and especially acute-carefully, with hypertonic saline (Algorithm II). Complications, such as cerebral edema, may develop if treatment is withheld.

References:

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