Hyponatremia:  

June 01, 2003
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ABSTRACT: Correction of chronic hyponatremia is associated with a very high risk of CNS complications; avoid a rapid increase in serum sodium concentration if you suspect a patient's condition is chronic. Thiazide- or metolazone-induced hyponatremia can develop rapidly—in 1 to 2 weeks—and its only presenting signs may be fatigue and listlessness. Diuretic-induced hyponatremia is 4 times as common in women as in men. Various factors greatly increase the risk of acute hyponatremia after surgery. Hyponatremia that develops after an operation which involves irrigation with a solution of glycine, mannitol, or sorbitol (such as transurethral prostatectomy [TURP] or hysteroscopy) may be hypertonic. An osmolar gap greater than 15 is a clue to this condition. Treatment of hypertonic hyponatremia in post-TURP or posthysteroscopy syndrome may require dialysis and a nephrology consult.

Pregnancy, use of thiazide diuretics, surgery—all can heighten the risk of hyponatremia. Here we offer treatment strategies tailored to these and other special settings. We also discuss the perils of overcorrection of serum sodium levels as well as the risks of undertreatment. Our article on page 861 provides a broader overview of both the diagnosis and management of hyponatremia and includes 2 algorithms that illustrate how we put our approach into practice.  

TREATMENT CAVEATS  

CNS sequelae. Central pontine myelinolysis (CPM) is a syndrome of irreversible demyelination of the pons that leads to spastic, disabling, long tract signs. The syndrome was first described about 40 years ago in patients who had been treated for hyponatremia with hypertonic saline. It is now referred to as "osmotic demyelination syndrome" (ODS), because some patients with "CPM" have a normal pons and demyelination in other areas of the brain. Since the syndrome was first identified, there has been much controversy over whether CPM, or ODS, is caused by the correction of hyponatremia (specifically, the rate of correction) or by a combination of hyponatremia, its correction, and serious comorbid conditions. There are 2 principal schools of thought on the issue. One school of thought, exemplified in a retrospective study by Sterns, holds that the risk of neurologic sequelae is associated with overly rapid correction; the other school, seen in a retrospective study by Ayus and colleagues, maintains that complications are associated with a final corrected sodium level that is too high rather than with the rate of correction.

In any event, the risk of CNS complications is inextricably linked to hyponatremia and its treatment. The risk of iatrogenic CNS injury is especially high with the correction of chronic hyponatremia. If you suspect that hyponatremia is chronic, keep in mind that overly rapid correction is much more dangerous than the hyponatremic state itself.

Hypoxia. Hyponatremic patients with hypoxia are especially prone to CNS injury. Prophylactic intubation is necessary in such patients to reduce the risk of cardiopulmonary arrest and resultant fatality or irreversible CNS injury. In patients with symptomatic hyponatremia, evaluate oxygen saturation and consider measuring blood gas levels as well. Avoid brain hypoxia of any degree whenever possible.

Postoperative hyponatremia. After surgery, all patients have elevated antidiuretic hormone (ADH) levels for multiple reasons (eg, the stress of the procedure, pain), as well as increased sympathetic tone, which further decreases water clearance. Moreover, increased levels of vasopressin (released by the hypothalamus in response to stress) and/or oxytocin (which is sometimes given to women postoperatively to constrict the blood vessels in the uterus) can have an antidiuretic effect. For these reasons, patients are prone to acute hyponatremia following surgery. In the past, the administration of hypotonic saline during the postoperative period further compounded the problem, although this practice has decreased significantly.

Post-TURP and posthysteroscopy syndromes. Transurethral prostatectomy (TURP) and
hysteroscopy pose special problems of electrolyte balance. During both procedures, the operative field may be irrigated with large volumes of fluids that contain glycine. Although glycine, mannitol, and sorbitol have all been used as irrigation fluid, a 200 mOsmol/L glycine solution is the most popular choice. Absorption of the irrigant fluid can cause severe acute hyponatremia. In one prospective study of TURP with glycine irrigation, 7% of the patients had severe hyponatremia (with serum sodium concentrations as low as 103 mEq/L) and one patient died. Because of the risk of morbidity and mortality, early diagnosis and treatment of post-TURP and posthysteroscopy hyponatremia are essential. Even vague complaints or slow mentation after these procedures mandate measurement of the serum sodium concentration. However, absorption of glycine irrigation solution often results in a hypertonic hyponatremia because of the extracellular excess of glycine; its metabolites (serine, glyoxylic acid, and oxalic acid); and ammonia, a by-product of glycine and serine deamination. This complicates treatment. Although administration of hypertonic saline might be an appropriate treatment choice for hypotonic hyponatremia, dialysis (and a nephrology consultation) may be required for hypertonic hyponatremia.

A good starting point for making therapeutic decisions in the post-TURP or posthysteroscopy setting is calculation of the osmolar gap. The osmolar gap is the difference between the actual measured osmolality (as determined by an osmometer) and the calculated osmolality, which is obtained by use of the following formula: 2(serum sodium concentration) + (serum glucose level)/18 + (blood urea nitrogen)/2.4 + (blood ethanol level)/4.6.

A difference greater than 15 indicates the presence of osmotic activity from exogenous solutes, such as glycine and glycine metabolites, and may suggest a treatment other than hypertonic saline.

**Endometrial ablation.** In addition to hysteroscopy, endometrial ablation is a procedure that carries special risks—especially as it becomes a more common alternative to hysterectomy for the treatment of dysfunctional uterine bleeding, menorrhagia, and leiomyoma. Large amounts of irrigation fluids may be administered during endometrial ablation—similar to the glycine irrigation used during hysteroscopy or TURP—and postoperative hyponatremic encephalopathy may result. The procedure is of particular concern because it is usually performed in menstruating women, the population at highest risk for morbidity and mortality from postoperative hyponatremia. To reduce this risk, Arieff and Ayus recommend the use of isotonic mannitol as an irrigation solution in place of the commonly used hypertonic preparations, and cautious—if any—use of oxytocin.

**TREATMENT TIPS FOR SPECIFIC PATIENT POPULATIONS**

**Women.** Awareness of gender differences is critical to correct diagnoses and successful treatment outcomes in tonicity disturbances. While either hyponatremia or its treatment can cause deleterious effects in any patient, the potential for a negative outcome is greater in women. Diuretic-induced hyponatremia is 4 times as common in women as in men, and menstruating women in whom postoperative hyponatremia causes neurologic symptoms are more likely than men to sustain permanent brain damage. Often, other causes of neurologic symptoms—such as subarachnoid hemorrhage, herpes encephalitis, and arteriovenous malformation—are suspected in premenopausal women who actually have symptomatic hyponatremia, and the correct diagnosis is thereby delayed. Women may be subject to invasive testing or treatment for other diseases while their sodium concentration is ignored.

The differences in the effects of hyponatremia in men and women may be the result of important gender differences in physiologic responses to changes in serum sodium concentration. Animal studies have shown females to have greater sensitivity to vasopressin than males and less ability to extrude sodium from brain cells than males have.

Sex hormones may play a role in mediating these different responses to hyponatremia. Estrogen has been shown to inhibit the sodium-potassium-ATPase responsible for sodium extrusion; androgens, on the other hand, augment its action. Also, ADH decreases brain production of adenosine triphosphate in women but not in men. Furthermore, estrogen has been shown to stimulate the release of vasopressin, which potentially increases water retention, while testosterone decreases ADH levels.

Preeclampsia may also predispose women to gender-related hyponatremia—which often goes unrecognized. Hayslett and colleagues have suggested that the impaired free-water clearance caused by the nephrotic syndrome, combined with the increased vasopressin levels that develop during pregnancy, may lead to hyponatremia in this setting. There have been several case reports of women with preeclampsia-related nephrotic syndrome whose serum sodium concentrations were as low as 121 mEq/L.

**Patients who take diuretics.** Thiazide- or metolazone-induced hyponatremia can develop...
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Hyponatremia: rapidly-in 1 to 2 weeks-and its only presenting signs may be vague complaints of fatigue and listlessness. This syndrome is associated with a mortality as high as 10%, and even patients who survive it are likely to sustain permanent neurologic sequelae caused by cerebral edema. Older patients who take metolazone or a thiazide diuretic need to be examined regularly for the development of hyponatremia. This is especially true if they have any complaints referable to the syndrome, no matter how vague.

**Patients with SIADH.** Some patients with severe syndrome of inappropriate antidiuretic hormone (SIADH) require alternative therapies, such as demeclocycline, that induce a nephrogenic diabetes insipidus with resultant water loss. Without such interventions, these patients may become severely hyponatremic and sustain cerebral edema.

**Patients with psychogenic polydipsia.** It is easy to overcorrect hyponatremia in patients with psychogenic polydipsia. Urine osmolality is already low in these patients, and they are in the process of "self-correction" for hyponatremia before treatment is even begun; thus, overcorrection, with the potential for CNS injury, can be a real hazard.

**Marathon runners.** A recent prospective study found that hyponatremia developed in 18% of 605 marathon runners. The women runners in the study with hyponatremia had lower serum sodium concentrations than their male counterparts. Another report documented the combination of hyponatremia, cerebral edema, and noncardiogenic pulmonary edema in 7 marathoners, one of whom died as a result. Not surprisingly, hyponatremia with serious morbidity has also been described in ultramarathoners. Always check electrolyte levels in a patient who collapses or feels ill after a long run (Box). Keep in mind that many of the signs and symptoms of exertional hyponatremia are identical to those of exertional heat stroke (eg, nausea, vomiting, extreme fatigue, respiratory distress, and CNS disturbances). However, the following symptoms can help distinguish exertional hyponatremia from other conditions:

- Progressively worsening headache.
- Normal exercise core temperature (generally less than 40°C [104°F]).
- Peripheral edema.

**References:**


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