TREATMENT HYPONATREMIA

Three major considerations guide the therapy of hyponatremia. First, the presence and/or severity of symptoms determine the urgency and goals of therapy. Patients with acute hyponatremia (Table 63-2) present with symptoms that can range from headache, nausea, and/or vomiting, to seizures, obtundation, and central herniation; patients with chronic hyponatremia, present for >48 h, are less likely to have severe symptoms. Second, patients with chronic hyponatremia are at risk for ODS if plasma Na^+ concentration is corrected by >8–10 m*M* within the first 24 h and/or by >18 m*M* within the first 48 h. Third, the response to interventions such as hypertonic saline, isotonic saline, or AVP antagonists can be highly unpredictable, such that frequent monitoring of plasma Na^+ concentration during corrective therapy is imperative.

Once the urgency in correcting the plasma Na^+ concentration has been established and appropriate therapy instituted, the focus should be on treatment or withdrawal of the underlying cause. Patients with euvolemic hyponatremia due to SIAD, hypothyroidism, or secondary adrenal failure will respond to successful treatment of the underlying cause, with an increase in plasma Na^+ concentration. However, not all causes of SIAD are immediately reversible, necessitating pharmacologic therapy to increase the plasma Na^+ concentration (see below). Hypovolemic hyponatremia will respond to intravenous hydration with isotonic normal saline, with a rapid reduction in circulating AVP and a brisk water diuresis; it may be necessary to reduce the rate of correction if the history suggests that hyponatremia has been chronic, i.e., present for more than 48 h (see below). Hypervolemic hyponatremia due to CHF will often respond to improved therapy of the underlying cardiomyopathy, e.g., following the institution or intensification of angiotensin-converting enzyme (ACE) inhibition. Finally, patients with hyponatremia due to beer potomania and low solute intake will respond very rapidly to intravenous saline and the resumption of a normal diet. Notably, patients with beer potomania have a very high risk of developing ODS, due to the associated hypokalemia, alcoholism, malnutrition, and high risk of overcorrecting the plasma Na^+ concentration.

Water deprivation has long been a cornerstone of the therapy of chronic hyponatremia. However, patients who are excreting minimal electrolyte-free water will require aggressive fluid restriction; this can be very difficult for patients with SIAD to tolerate, given that their thirst is also inappropriately stimulated. The urine-to-plasma electrolyte ratio (urinary $[Na^+] + [K^+]$/plasma $[Na^+]$) can be exploited as a quick indicator of electrolyte-free water excretion **(Table 63-3)**; patients with a ratio of >1 should be more aggressively restricted (<500 mL/d), those with a ratio of ~1 should be restricted to 500–700 mL/d, and those with a ratio <1 should be restricted to <1 L/d. In hypokalemic patients, potassium replacement will serve to increase plasma Na^+ concentration, given that the plasma Na^+ concentration is a functional of both exchangeable Na^+ and exchangeable K^+ divided by total-body water; a corollary is that aggressive repletion of K^+ has the potential to overcorrect the plasma Na^+ concentration even in the absence of hypertonic saline. Plasma Na^+ concentration will also tend to respond to an increase in dietary solute intake, which increases the ability to excrete free water; however, the use of oral urea and/or salt tablets for this purpose is generally not practical or well tolerated.

Patients in whom therapy with fluid restriction, potassium replacement, and/or increased solute intake fails may merit pharmacologic therapy to increase their plasma Na^+ concentration. Many patients with SIAD respond to combined therapy with oral furosemide, 20 mg twice a day (higher doses may be necessary in renal insufficiency), and oral salt tablets; furosemide serves to inhibit the renal countercurrent mechanism and blunt urinary concentrating ability, whereas the salt tablets counteract diuretic-associated natriuresis. Demeclocycline is a potent inhibitor of principal cells and can be used in patients whose Na levels do not increase in response to furosemide and salt tablets. However, this agent can be associated with a reduction in GFR, due to excessive natriuresis and/or direct renal toxicity; it should be avoided in cirrhotic patients in particular, who are at higher risk of nephrotoxicity due to drug accumulation.

AVP antagonists (vaptans) are highly effective in SIAD and in hypervolemic hyponatremia due to heart failure or cirrhosis, reliably increasing plasma Na^+ concentration due to their "aquaretic" effects (augmentation of free water clearance). Most of these agents specifically antagonize the V_2 AVP receptor; tolvaptan is currently the only oral V_2 antagonist to be approved by the U.S. Food and Drug Administration. Conivaptan, the only available intravenous vaptan, is a mixed V_{1A}/V_2 antagonist, with a modest risk of hypotension due to V_{1A} receptor inhibition. Therapy with vaptans must be initiated in a hospital setting, with a liberalization of fluid restriction (>2 L/d) and close monitoring of plasma Na^+ concentration. Although approved for the management of all but hypovolemic hyponatremia and acute hyponatremia, the clinical indications for these agents are not completely clear. Oral tolvaptan is perhaps most appropriate for the management of significant and persistent SIAD (e.g., in small-cell lung carcinoma) that has not responded to water restriction and/or oral furosemide and salt tablets. Abnormalities in liver function tests have been reported with chronic tolvaptan therapy; hence, the use of this agent should be restricted to <1–2 months.

Treatment of acute symptomatic hyponatremia should include hypertonic 3% saline (513 m*M*) to acutely increase plasma Na^+ concentration by 1–2 m*M*/h to a total of 4–6 m*M*; this modest increase is typically sufficient to alleviate severe acute symptoms, after which corrective guidelines for chronic hyponatremia are appropriate (see below). A number of equations have been developed to estimate the required rate of hypertonic saline, which has an Na^+-Cl^- concentration of 513 m*M*. The traditional approach is to calculate an Na^+ deficit, where the Na^+ deficit = 0.6 × body weight × (target plasma Na^+ concentration – starting plasma Na^+ concentration), followed by a calculation of the required rate. Regardless of the method used to determine the rate of administration, the increase in plasma Na^+ concentration can be highly unpredictable during treatment with hypertonic saline, due to rapid changes in the underlying physiology; plasma Na^+ concentration should be monitored every 2–4 h during treatment, with appropriate changes in therapy based on the observed rate of change. The administration of supplemental oxygen and ventilatory support is also critical in acute hyponatremia, in the event that patients develop acute pulmonary edema or hypercapneic respiratory failure. Intravenous loop diuretics will help treat acute pulmonary edema and will also increase free water excretion, by interfering with the renal countercurrent multiplication system. AVP antagonists do *not* have an approved role in the management of acute hyponatremia.

TABLE 63-3 MANAGEMENT OF HYPERNATREMIA

Water Deficit
1. Estimate total-body water (TBW): 50% of body weight in women and 60% in men
2. Calculate free-water deficit: $[(Na^+ - 140)/140] \times TBW$
3. Administer deficit over 48–72 h, without decrease in plasma Na^+ concentration by >10 m*M*/24 h
Ongoing Water Losses
4. Calculate free-water clearance, C_eH_2O: $$C_eH_2O = V \times \left(1 - \frac{U_{Na} + U_K}{P_{Na}}\right)$$ where V is urinary volume, U_{Na} is urinary $[Na^+]$, U_K is urinary $[K^+]$, and P_{Na} is plasma $[Na^+]$
Insensible Losses
5. ~10 mL/kg per day: less if ventilated, more if febrile
Total
6. Add components to determine water deficit and ongoing water loss; correct the water deficit over 48–72 h and replace daily water loss. Avoid correction of plasma $[Na^+]$ by >10 m*M*/d.