aggressive water restriction would have theoretically been successful; however, this can be very difficult for patients with SIAD to tolerate, given that their thirst is also inappropriately stimulated.

Combined therapy with furosemide and salt tablets can often increase the plasma Na^+ concentration in SIAD; furosemide reduces maximal urinary concentrating ability by inhibiting the countercurrent mechanism, whereas the salt tablets mitigate diuretic-associated NaCl loss and amplify the ability to excrete free water by increasing urinary solute excretion. This regimen is not always successful and requires careful titration of salt tablets to avoid volume depletion; indeed, in this particular patient, the plasma Na^+ concentration remained <130 meq/L and the patient became orthostatic. The principal cell toxin, demeclocycline, is an alternative oral agent in SIAD. Treatment with demeclocycline was very successful in this patient, with an increase in plasma Na^+ concentration to 140 meq/L. However, demeclocycline can be natriuretic, leading to a prerenal decrease in GFR. Demeclocycline has also been implicated in nephrotoxic injury, particularly in patients with cirrhosis and chronic liver disease, in whom the drug accumulates. Notably, this particular patient developed a significant but stable decrease in GFR while on demeclocycline, necessitating a reduction in the administered dose.

A major advance in the management of hyponatremia was the clinical development of AVP antagonists (vaptans). These agents inhibit the effect of AVP on renal V_2 receptors, resulting in the excretion of electrolyte-free water and correction of hyponatremia. The specific indications for these agents are not as yet clear, despite U.S. Food and Drug Administration (FDA) approval for the management of both euvolemic and hypervolemic hyponatremia. It is, however, anticipated that the vaptans will have an increasing role in the management of SIAD and other causes of hyponatremia. Indeed, if this particular patient had continued with active therapy for his cancer, substitution of demeclocycline with oral tolvaptan (a V_2-specific oral vaptan) would have been the next appropriate step, given the development of renal insufficiency with demeclocycline. As with other measures to correct hyponatremia (e.g., hypertonic saline, demeclocycline), the vaptans have the potential to "overcorrect" plasma Na^+ concentration (a rise of >8–10 meq/L per 24 h or 18 meq/L per 18 h), thus increasing the risk for osmotic demyelination (see Case 5). Therefore, the plasma Na^+ concentration should be monitored closely during the initiation of therapy with these agents. In addition, long-term use of tolvaptan has been associated with abnormalities in liver function tests; hence, use of this agent should be restricted to only 1–2 months.

CASE 5

A 76-year-old woman presented with a several-month history of diarrhea, with marked worsening over the 2–3 weeks before admission (up to 12 stools a day). Review of systems was negative for fever, orthostatic dizziness, nausea and vomiting, or headache. Past medical history included hypertension, kidney stones, and hypercholesterolemia; medications included atenolol, spironolactone, and lovastatin. She also reliably consumed >2 L of liquid per day in management of the nephrolithiasis.

The patient received 1 L of saline over the first 5 h of her hospital admission. On examination at hour 6, the heart rate was 72 sitting and 90 standing, and blood pressure was 105/50 mmHg lying and standing. Her jugular venous pressure (JVP) was indistinct with no peripheral edema. On abdominal examination, the patient had a slight increase in bowel sounds but a nontender abdomen and no organomegaly.

The plasma Na^+ concentration on admission was 113 meq/L, with a creatinine of 2.35 (Table 64e-1). At hospital hour 7, the plasma Na^+ concentration was 120 meq/L, potassium 5.4 meq/L, chloride 90 meq/L, bicarbonate 22 meq/L, BUN 32 mg/dL, creatinine 2.02 mg/dL, glucose 89 mg/dL, total protein 5.0, and albumin 1.9. The hematocrit was 33.9, white count 7.6, and platelets 405. A morning cortisol was 19.5, with thyroid-stimulating hormone (TSH) of 1.7. The patient was treated with 1 μg of intravenous DDAVP, along with 75 mL/h of intravenous half-normal saline. After the plasma Na^+ concentration dropped to 116 meq/L, intravenous fluid was switched to normal saline at the same infusion rate. The subsequent results are shown in Table 64e-1.

TABLE 64e-1 SERIAL LABORATORY DATA FOR CASE 5

Hospital Hour	Baseline	0	3	7	11	14	24	48	72
Plasma Na^+ (meq/L)	137	113	115	120	117	116	117	124	130
Creatinine (mg/dL)	1.2	2.35	2.10	2.02	1.97	1.79	1.53	1.20	1.13
Urine osmolality (mOsm/kg)				319		415	397		
Urine Na^+ (meq/L)				17		23	47		

APPROACH TO DIAGNOSIS

This patient presented with hypovolemic hyponatremia and a "prerenal" reduction in GFR, with an increase in serum creatinine. She had experienced diarrhea for some time and manifested an orthostatic tachycardia after a liter of normal saline. As expected for hypovolemic hyponatremia, the urine Na^+ concentration was <20 meq/L in the absence of congestive heart failure or other causes of hypervolemic hyponatremia, and she responded to saline hydration with an increase in plasma Na^+ concentration and a decrease in creatinine.

The initial hypovolemia increased the sensitivity of this patient's AVP response to osmolality, both decreasing the osmotic threshold for AVP release and increasing the slope of the osmolality response curve. AVP has a half-life of only 10–20 min; therefore, the acute increase in intravascular volume after a liter of intravenous saline led to a rapid reduction in circulating AVP. The ensuing water diuresis is the primary explanation for the rapid increase in plasma Na^+ concentration in the first 7 h of her hospitalization.

APPROACH TO MANAGEMENT

The key concern in this case was the evident chronicity of the patient's hyponatremia, with several weeks of diarrhea followed by 2–3 days of acute exacerbation. This patient was judged to have chronic hyponatremia, i.e., with a suspected duration of >48 h; as such, she would be predisposed to osmotic demyelination were she to undergo too rapid a correction in her plasma Na^+ concentration, i.e., by >8–10 meq/L in 24 h or 18 meq/L in 48 h. At presentation, she had no symptoms that one would typically attribute to acute hyponatremia, and the plasma Na^+ concentration had already increased by a sufficient amount to protect from cerebral edema; however, she had corrected by 1 meq/L per hour within the first 7 h of admission, consistent with impending overcorrection. To reduce or halt the increase in plasma Na^+ concentration, the patient received 1 μg of intravenous DDAVP along with intravenous free water. Given the hypovolemia and resolving acute renal insufficiency, a decision was made to administer half-normal saline as a source of free water, rather than D_5W; this was switched to normal saline when plasma Na^+ concentration acutely dropped to 117 meq/L (Table 64e-1).

Overcorrection of chronic hyponatremia is a major risk factor for the development of osmotic demyelination syndrome (ODS). Animal studies show a neurologic and survival benefit in ODS of "re-lowering" plasma Na^+ concentration with DDAVP and free water administration; this approach is demonstrably safe in patients with hyponatremia, with no evident risk of seizure or other sequelae. This combination can be used to prevent an overcorrection or to re-lower plasma Na^+ concentration in patients who have already overcorrected. DDAVP is required because in most of these patients endogenous AVP levels have plummeted, resulting in a free water diuresis; the administration of free water alone has minimal effect in this setting, given the relative absence of circulating AVP. An alternative approach in patients who present with severe hyponatremia is to treat them prospectively with twice-daily DDAVP to prevent changes in AVP bioactivity, coadministering hypertonic saline to increase slowly the plasma Na^+ concentration in a more controlled fashion.

This patient's plasma Na^+ concentration remained depressed for several days after DDAVP administration. It is