TABLE 404-3 DIFFERENTIAL DIAGNOSIS OF HYPONATREMIA BASED ON CLINICAL ASSESSMENT OF EXTRACELLULAR FLUID VOLUME (ECFV)

Clinical Findings	Type I, Hypervolemic	Type II, Hypovolemic	Type III, Euvolemic	SIADH and SIAD Euvolemic
History				
CHF, cirrhosis, or nephrosis	Yes	No	No	No
Salt and water loss	No	Yes	No	No
ACTH–cortisol deficiency and/or nausea and vomiting	No	No	Yes	No
Physical examination				
Generalized edema, ascites	Yes	No	No	No
Postural hypotension	Maybe	Maybe	Maybe[a]	No
Laboratory				
BUN, creatinine	High-normal	High-normal	Low-normal	Low-normal
Uric acid	High-normal	High-normal	Low-normal	Low-normal
Serum potassium	Low-normal	Low-normal[b]	Normal[c]	Normal
Serum urate	High	High	Low	Low
Serum albumin	Low-normal	High-normal	Normal	Normal
Serum cortisol	Normal-high	Normal-high[d]	Low[e]	Normal
Plasma renin activity	High	High	Low[f]	Low
Urinary sodium (meq per unit of time)[g]	Low	Low[h]	High[i]	High[i]

[a]Postural hypotension may occur in secondary (ACTH-dependent) adrenal insufficiency even though extracellular fluid volume and aldosterone are usually normal. [b]Serum potassium may be high if hypovolemia is due to aldosterone deficiency. [c]Serum potassium may be low if vomiting causes alkalosis. [d]Serum cortisol is low if hypovolemia is due to primary adrenal insufficiency (Addison's disease). [e]Serum cortisol will be normal or high if the cause is nausea and vomiting rather than secondary (ACTH-dependent) adrenal insufficiency. [f]Plasma renin activity may be high if the cause is secondary (ACTH) adrenal insufficiency. [g]Urinary sodium should be expressed as the *rate of excretion* rather than the concentration. In a hyponatremic adult, an excretion rate >25 meq/d (or 25 μeq/mg of creatinine) could be considered high. [h]The rate of urinary sodium excretion may be high if the hypovolemia is due to diuretic abuse, primary adrenal insufficiency, or other causes of renal sodium wasting. [i]The rate of urinary sodium excretion may be low if intake is curtailed by symptoms or treatment.

Abbreviations: ACTH, adrenocorticotropic hormone; BUN, blood urea nitrogen; CHF, congestive heart failure; SIAD, syndrome of inappropriate antidiuresis.

output, and serum sodium should be checked at least once every 2h to ensure it is not raised too fast or too far. Doing so may result in central pontine myelinolysis, an acute, potentially fatal neurologic syndrome characterized by quadriparesis, ataxia, and abnormal extraocular movements.

In chronic and/or minimally symptomatic SIADH, the hyponatremia can and should be corrected more gradually. This can be achieved by restricting total fluid intake to less than the sum of urinary and insensible losses. Because the water derived from food (300–700 mL/d) usually approximates basal insensible losses in adults, the aim should be to reduce total discretionary intake (all liquids) to approximately 500 mL less than urinary output. Adherence to this regimen is often problematic and, even if achieved, usually reduces body water and increases serum sodium by only about 1–2% per day. Hence, additional approaches are usually desirable if not necessary. The best approach for treatment of chronic SIADH is the administration of an oral vaptan, tolvaptan, a selective V_2 antagonist that also increases urinary water excretion by blocking the antidiuretic effect of AVP. Some restriction of fluid intake may also be necessary to achieve satisfactory control of the hyponatremia. It is approved for treatment of nonemergent SIADH with initial in-hospital dosing. Other approaches include demeclocycline, 150–300 mg PO tid or qid, or fludrocortisone, 0.05–0.2 mg PO bid. The effect of the demeclocycline manifests in 7–14 days and is due to induction of a reversible form of nephrogenic DI. Potential side effects include phototoxicity and azotemia. The effect of fludrocortisone also requires 1–2 weeks and is partly due to increased retention of sodium and possibly inhibition of thirst. It also increases urinary potassium excretion, which may require replacement through dietary adjustments or supplements and may induce hypertension, occasionally necessitating discontinuation of the treatment.

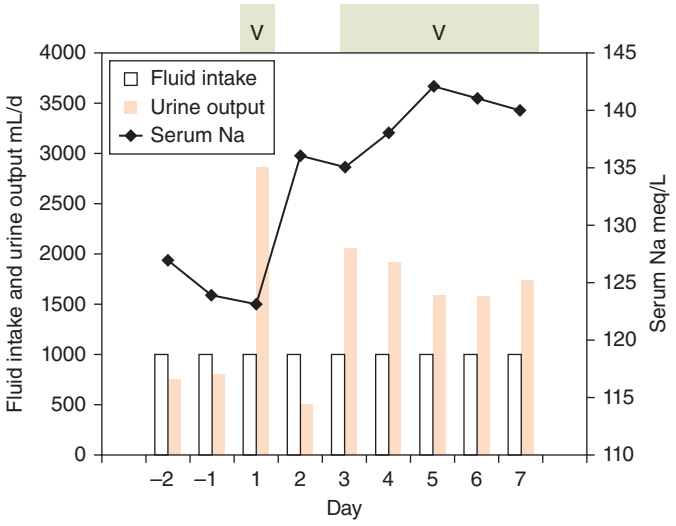

FIGURE 404-7 The effect of vaptan therapy on water balance in a patient with chronic syndrome of inappropriate antidiuretic hormone (SIADH). The periods of vaptan (V) therapy are indicated by the green shaded boxes at the top. Urine output is indicated by orange bars. Fluid intake is shown by the open bars. Intake was restricted to 1 L/d throughout. Serum sodium is indicated by the black line. Note that sodium increased progressively when vaptan increased urine output to levels that clearly exceeded fluid intake.

In euvolemic hyponatremia caused by protracted nausea and vomiting or isolated glucocorticoid deficiency (type III), all abnormalities can be corrected quickly and completely by giving an antiemetic or stress doses of hydrocortisone (for glucocorticoid deficiency). As with other treatments, care must be taken to ensure that serum sodium does not rise too quickly or too far.

In SIAD due to an activating mutation of the V_2 receptor, the V_2 antagonists usually do not block the antidiuresis or raise plasma osmolarity/sodium. In that condition, use of an osmotic diuretic such as urea is reported to be effective in preventing or correcting hyponatremia. However, some vaptans may be effective in patients with a different type of activating mutation so the response to this therapy may be neither predictable nor diagnostic.

In hypervolemic hyponatremia, fluid restriction is also appropriate and somewhat effective if it can be maintained. However,