exacerbating lithium-associated polyuria. The entry of lithium through the amiloride-sensitive Na^+ channel ENaC (Fig. 64e-1) is required for the effect of the drug on principal cells, such that combined therapy with lithium and amiloride can mitigate lithium-associated NDI. However, lithium causes chronic tubulointerstitial scarring and chronic kidney disease after prolonged therapy, such that patients may have a persistent NDI long after stopping the drug, with a reduced therapeutic benefit from amiloride. Notably, this particular patient had been treated intermittently for several years with lithium, with the development of chronic kidney disease (baseline creatinine of 1.3–1.4) and NDI that persisted after stopping the drug.

APPROACH TO MANAGEMENT

How should this patient be treated? What are the major pitfalls of therapy?

This patient developed severe hypernatremia due to a water diuresis from lithium-associated NDI. Treatment of hypernatremia must include both replacement of the existing free water deficit and daily replacement of ongoing free water loss. The first step is to estimate total-body water (TBW), typically estimated as 50% of the body weight in women and 60% in men. The free water deficit is then calculated as $([Na^+ - 140]/140) \times TBW$. In this patient, the free water deficit was 4.2 L at a weight of 97.5 kg and plasma Na^+ concentration of 150 meq/L. This free water deficit should be replaced slowly over 48–72 h to avoid increasing the plasma Na^+ concentration by >10 meq/L per 24 h. A common mistake is to replace this deficit while neglecting to replace ongoing losses of free water, such that plasma Na^+ concentration either fails to correct or, in fact, increases.

Ongoing losses of free water can be estimated using the equation for electrolyte-free water clearance:

$$C_eH_2O = V\,(1 - [U_{Na}+U_K]/P_{Na})$$

where V is urinary volume, U_{Na} is urinary $[Na^+]$, U_K is urinary $[K^+]$, and P_{Na} is plasma $[Na^+]$.

For this patient, the C_eH_2O was 2.5 L/d when initially evaluated, i.e., with urine Na^+ and K^+ concentrations of 34 and 5.2 meq/L, plasma Na^+ concentration of 150 meq/L, and a urinary volume of 3.4 L. Therefore, the patient was given 2.5 L of D_5W over the first 24 h to replace ongoing free water losses, along with 2.1 L of D_5W to replace half his free water deficit. Daily random urine electrolytes and urinary volume measurement can be used to monitor C_eH_2O and adjust daily fluid administration in this manner, while following plasma Na^+ concentration. Physicians often calculate the free water deficit to guide therapy of hypernatremia, providing half the deficit in the first 24 h. This approach can be adequate in patients who do not have significant ongoing losses of free water, e.g., with hypernatremia due to decreased free water intake. This case illustrates how free water requirements can be grossly underestimated in hypernatremic patients if ongoing, daily free water losses are not taken into account.

CASE 4

A 78-year-old man was admitted with pneumonia and hyponatremia. Plasma Na^+ concentration was initially 129 meq/L, decreasing within 3 days to 118–120 meq/L despite fluid restriction to 1 L/d. A chest computed tomography (CT) revealed a right 2.8 × 1.6 cm infrahilar mass and postobstructive pneumonia. The patient was an active smoker. Past medical history was notable for laryngeal carcinoma treated 15 years prior with radiation therapy, renal cell carcinoma, peripheral vascular disease, and hypothyroidism. On review of systems, he denied headache, nausea, and vomiting. He had chronic hip pain, managed with acetaminophen with codeine. Other medications included cilostazol, amoxicillin/clavulanate, digoxin, diltiazem, and thyroxine. He was euvolemic on examination, with no lymphadenopathy and a normal chest examination.

Laboratory Data						
Na^+ 120	K^+ 4.3	Cl^- 89	HCO_3^- 23	BUN 8	Creat 1.0	Glu 93
Alb 3.1	Ca 8.9	Phos 2.8	Mg 2.0	Plasma osm 248 mOsm/kg		
Cortisol 25 μg/dL		TSH 2.6	Uric acid 2.7 mg/dL			
Urine:	Na^+ 97	K^+ 22	Cl^- 86	Osm 597		

The patient was treated with furosemide, 20 mg PO bid, and salt tablets. The plasma Na^+ concentration increased to 129 meq/L with this therapy; however, the patient developed orthostatic hypotension and dizziness. He was started on demeclocycline, 600 mg PO in the morning and 300 mg in the evening, just before discharge from hospital. Plasma Na^+ concentration increased to 140 meq/L with a BUN of 23 and creatinine of 1.4, at which point demeclocycline was reduced to 300 mg PO bid. Bronchoscopic biopsy eventually showed small-cell lung cancer; the patient declined chemotherapy and was admitted to hospice.

APPROACH TO DIAGNOSIS AND MANAGEMENT

What factors contributed to this patient's hyponatremia? What are the therapeutic options?

This patient developed hyponatremia in the context of a central lung mass and postobstructive pneumonia. He was clinically euvolemic, with a generous urine Na^+ concentration and low plasma uric acid concentration. He was euthyroid, with no evidence of pituitary dysfunction or secondary adrenal insufficiency. The clinical presentation is consistent with the syndrome of inappropriate antidiuresis (SIAD). Although pneumonia was a potential contributor to the SIAD, it was notable that the plasma Na^+ concentration decreased despite a clinical response to antibiotics. It was suspected that this patient had SIAD due to small-cell lung cancer, with a central lung mass on chest CT and a significant smoking history. There was a history of laryngeal cancer and renal cancer but with no evidence of recurrent disease; these malignancies were not considered contributory to his SIAD. Biopsy of the lung mass ultimately confirmed the diagnosis of small-cell lung cancer, which is responsible for ~75% of malignancy-associated SIAD; ~10% of patients with this neuroendocrine tumor will have a plasma Na^+ concentration of <130 meq/L at presentation. The patient had no other "nonosmotic" stimuli for an increase in AVP, with no medications associated with SIAD and minimal pain or nausea.

The patient had no symptoms attributable to hyponatremia but was judged at risk for worsening hyponatremia from severe SIAD. Persistent, chronic hyponatremia (duration >48 h) results in an efflux of organic osmolytes (creatine, betaine, glutamate, myoinositol, and taurine) from brain cells; this response reduces intracellular osmolality and the osmotic gradient favoring water entry. This cellular response does not fully protect patients from symptoms, which can include vomiting, nausea, confusion, and seizures, usually at plasma Na^+ concentration <125 meq/L. Even patients who are judged "asymptomatic" can manifest subtle gait and cognitive defects that reverse with correction of hyponatremia. Chronic hyponatremia also increases the risk of bony fractures due to an increased risk of falls and to a hyponatremia-associated reduction in bone density. Therefore, every attempt should be made to correct plasma Na^+ concentration safely in patients with chronic hyponatremia. This is particularly true in malignancy-associated SIAD, where it can take weeks to months for a tissue diagnosis and the subsequent reduction in AVP following initiation of chemotherapy, radiotherapy, and/or surgery.

What are the therapeutic options in SIAD? Water deprivation, a cornerstone of therapy for SIAD, had little effect on the plasma Na^+ concentration in this patient. The urine:plasma electrolyte ratio (urinary $[Na^+] + [K^+]$/plasma $[Na^+]$) can be used to estimate electrolyte-free water excretion and the required degree of water restriction; 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. This patient had a urine:plasma electrolyte ratio of 1 and predictably did not respond to a moderate water restriction of ~1 L/d. A more