CHAPTER e15

Fluid and Electrolyte Imbalances and Acid-Base Disturbances: Case Examples

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CASE 1

A 23-year-old woman was admitted with a 3-day history of fever, cough productive of blood-tinged sputum, confusion, and orthostasis. Past medical history included Type I diabetes mellitus. A physical examination in the emergency department indicated postural hypotension, tachycardia, and Kussmaul respiration, and the breath was noted to smell of "acetone." Examination of the thorax suggested consolidation in the right lower lobe.

Laboratory Data		Units
Na^+	130	meq/L
K^+	5.0	meq/L
Cl^-	96	meq/L
CO_2	14	meq/L
Blood urea nitrogen (BUN)	20	mg/dL
Creatinine (Creat)	1.3	mg/dL
Glucose	450	mg/dL
Arterial Blood Gases	**On Room Air**	
pH	7.39	
P_{CO_2}	24	mmHg
Pa_{O_2}	89	mmHg
HCO_3^-	14	meq/L
Anion gap	20	meq/L
Urinalysis		
Urine ketones	Positive 4+	
Glucose	Positive 4+	
Serum ketones	Strongly positive 1:8	
Chest x-ray		
Pneumonic infiltrate, right lower lobe		

APPROACH TO DIAGNOSIS

The diagnosis of the acid-base disorder should proceed in a stepwise fashion:

1. The normal anion gap (AG) is 10 meq/L, but in this case the anion gap is elevated (20 meq/L). Therefore, the change in AG (ΔAG) = 10 meq/L.
2. Compare the ΔAG and the $\Delta[HCO_3^-]$. In this case, the ΔAG, as noted above, is 10 and the $\Delta[HCO_3^-]$ (25 – 14) is 11. Therefore, the increment in the anion gap is approximately equal to the decrement in bicarbonate.
3. The next step is to estimate the respiratory compensatory response. In this case, the predicted Pa_{CO_2} for an $[HCO_3^-]$ of 14 should be approximately 29 mmHg. This value is obtained by adding 15 to the measured $[HCO_3^-]$ (15 + 14 = 29) or by calculating the predicted Pa_{CO_2} from the Winter equation: $1.5 \times [HCO_3^-] + 8$. In either case, the predicted value for Pa_{CO_2} of 29 is significantly higher than the measured value of 24. Therefore, the prevailing Pa_{CO_2} exceeds the range for compensation alone and is too low.
4. Therefore, this patient has a mixed acid-base disturbance with two components: (a) high anion-gap acidosis secondary to ketoacidosis and (b) respiratory alkalosis secondary to community-acquired pneumonia. The respiratory alkalosis resulted in an additional component of hyperventilation that exceeded the compensatory response driven by metabolic acidosis, explaining the normal pH in this case. The finding of respiratory alkalosis in the setting of a high-gap acidosis suggests another cause of the respiratory component, which in this case may be attributed to the community-acquired pneumonia.

The clinical features in this case include hyperglycemia, hypovolemia, ketoacidosis, central nervous system (CNS) signs of confusion, and superimposed pneumonia. This clinical scenario is consistent with diabetic ketoacidosis (DKA) developing in a patient with known Type I diabetes mellitus. Infections in DKA are common and may be a precipitating feature in the development of ketoacidosis.

The diagnosis of DKA is usually not challenging but should be considered in all patients with an elevated anion-gap and metabolic acidosis. Hyperglycemia and ketonemia (positive acetoacetate at a dilution of 1:8 or greater) are sufficient criteria for diagnosis in patients with Type 1 diabetes mellitus. The $\Delta[HCO_3^-]$ should approximate the increase in the plasma anion gap (ΔAG), but this equality can be modified by several factors. For example, the ΔAG often decreases with IV hydration, as glomerular filtration increases and ketones are excreted into the urine. The decrement in plasma sodium results from hyperglycemia, which induces the movement of water into the extracellular compartment from the intracellular compartment of cells that require insulin for the transport of glucose. Additionally, a natriuresis occurs in response to an osmotic diuresis associated with hyperglycemia. Moreover, in patients with DKA, thirst is very common and water ingestion often continues. The plasma potassium concentration is usually mildly elevated, but in the face of acidosis and as a result of the ongoing osmotic diuresis, a significant total-body deficit of potassium is almost always present. Recognition of this total-body deficit is critically important. The inclusion of potassium replacement in the therapeutic regimen at the appropriate time and with the appropriate indications (see below) is essential. Volume depletion is a very common finding in diabetic ketoacidosis and is a pivotal component in the pathogenesis of the disorder.

APPROACH TO MANAGEMENT

Patients with diabetic ketoacidosis often have a sustained and significant deficit of sodium, potassium, water, bicarbonate, and phosphate. The general approach to treatment requires attention to all those abnormalities. Successful treatment of DKA involves a stepwise approach, as follows:

1. *Replace extracellular fluid (ECF) volume deficits.* Since most patients present with actual or relative hypotension and, at

times, impending shock, the initial fluid administered should be 0.9% NaCl infused rapidly until the systolic blood pressure is >100 mmHg or until 2–3 L cumulatively has been administered. During the initial 2–3 h of infusion of saline, the decline in blood glucose can be accounted for by dilution and increased renal excretion. Glucose should be added to the infusion as D_5 NS or D_5 0.45% NS once the plasma glucose declines to 230 mg/dL or less.

2. *Abate the production of ketoacids.* Regular insulin is required during diabetic ketoacidosis as an initial bolus of 0.1 U/kg body weight (BW) IV followed immediately by a continuous infusion of 0.1 U/kg BW per h in NS. The effectiveness of IV (not subcutaneous) insulin can be tracked by observing the decline in plasma ketones. Since the increment in the anion gap above the normal value of 10 meq/L represents accumulated ketoacids in DKA, the disappearance of ketoacid anions is reflected by the narrowing and eventual normalization of the anion gap. Typically, the plasma anion gap returns to normal within 8–12 h.
3. *Replace potassium deficits.* Although patients with DKA often have hyperkalemia due to insulin deficiency, they are usually severely K^+ depleted. KCl (20 meq/L) should be added to each liter of IV fluids when urine output is established and after insulin has been administered.
4. *Correct the metabolic acidosis.* The plasma bicarbonate concentration usually will not increase for several hours because of dilution from administered IV NaCl. The plasma [HCO^-] approaches 18 meq/L once ketoacidosis disappears. Sodium bicarbonate therapy often is not recommended, especially in children. Bicarbonate is administered to adults with DKA for extreme acidemia (pH <7.1); for elderly patients (>70 years), a threshold pH of 7.20 is recommended. Sodium bicarbonate, if administered, should be given only in small amounts. Since ketoacids are metabolized after insulin therapy, bicarbonate will be added to the ECF. Overshoot alkalosis may result from the combination of exogenously administered sodium bicarbonate and metabolic production of bicarbonate.
5. *Phosphate.* In the first 6–8 h of therapy, it may be necessary to infuse potassium with phosphate because of the unmasking of phosphate depletion during combined insulin and glucose therapy. The latter drives phosphate into the cell. Therefore, in patients with DKA, the plasma phosphate level should be followed closely but phosphate should never be replaced empirically. Phosphate should be administered to patients with a declining plasma phosphate once the phosphate level declines into the low-normal level. Therapy is advisable in the form of potassium phosphate at a rate of 6 mmol/h.
6. Always seek *underlying factors* such as infection, myocardial infarction, pancreatitis, cessation of insulin therapy, or other events that are responsible for initiating diabetic ketoacidosis. The case presented here is illustrative of this point.
7. Volume overexpansion with IV fluid administration is not uncommon and contributes to the development of hyperchloremic acidosis during the later stages of treatment of DKA. *Volume overexpansion should be avoided.*

CASE 2

A 25-year-old man with a 6-year history of HIV/AIDS complicated recently by *Pneumocystis jiroveci* pneumonia (PCP) was treated with intravenous trimethoprim-sulfamethoxazole (20 mg TMP/kg per day). On day 4 of treatment, the following laboratory data were obtained:

Laboratory Data	Units	Plasma	Urine
Na^+	meq/L	135	60
K^+	meq/L	6.5	15
Cl^-	meq/L	110	43
HCO_3^-	meq/L	15	0
pH		7.30	5.5
BUN	mg/dL	14	—
Creat	mg/dL	0.9	—
Osmolality	mOsmol/kg H_2O	268	270

APPROACH TO DIAGNOSIS

What caused the hyperkalemia and metabolic acidosis in this patient? What other medications may be associated with a similar presentation? How does one utilize the urine electrolyte data to determine whether the hyperkalemia is of renal origin or is due to a shift from the cell to the extracellular compartment?

Hyperkalemia occurs in 15–20% of hospitalized patients with HIV/AIDS. The usual causes are adrenal insufficiency, the syndrome of hyporeninemic hypoaldosteronism, or one of several drugs, including trimethoprim, pentamidine, nonsteroidal anti-inflammatory drugs, angiotension-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers, spironolactone, and eplerenone. Trimethoprim usually is given in combination with sulfamethoxazole or dapsone for PCP and on average increases the plasma K^+ concentration by about 1 meq/L; however, the hyperkalemia may be severe. Trimethoprim is structurally and chemically related to amiloride and triamterene and in this way may function as a potassium-sparing diuretic. This effect is caused by inhibition of the epithelial sodium channel (ENaC) in the principal cell of the collecting duct. When the Na^+ channel is blocked, K^+ secretion also is inhibited; K^+ secretion is dependent on the lumen-negative potential difference generated by Na^+ entry through ENaC (Fig. e15-1).

TMP is associated with a non-anion-gap acidosis that parallels the development of hyperkalemia such that the co-occurrence of hyperkalemia and metabolic acidosis is not uncommon in this setting. H^+ secretion via apical H^+-ATPase pumps in adjacent type A intercalated cells (Fig. e15-1) is also electrogenic so that the reduction in the lumen-negative potential difference due to TMP inhibits distal H^+ secretion; this often is referred to as a voltage defect form of distal renal tubular acidosis. Systemic hyperkalemia also suppresses renal ammoniagenesis, ammonium excretion, and thus acid excretion; i.e., hyperkalemia *per se* has multiple effects on urinary acidification.

The inhibitory effect of trimethoprim on K^+ and H^+ secretion in the cortical collecting tubule follows a dose-response relationship; therefore, the higher doses of this agent used in HIV/AIDS patients with PCP or in deep tissue infections with methicillin-resistant *Staphylococcus aureus* (MRSA) result in a higher prevalence of hyperkalemia and acidosis. Conventional doses of trimethoprim also can induce hyperkalemia and/or acidosis in predisposed patients, in particular the elderly, patients with renal insufficiency, and/or those with baseline hyporeninemic hypoaldosteronism.

One means by which to assess the role of the kidney in the development of hyperkalemia is to calculate, from a spot urine and coincident plasma sample, the transtubular potassium gradient (TTKG). The TTKG is calculated as $(P_{osmol} \times U_{Potassium})/(P_{Potassium} \times U_{osmol})$. The expected values of the TTKG are <3 in the presence of hypokalemia (see also Case 7 and Case 8) and >7–8 in the presence of hyperkalemia. In this case, the value for the TTKG of approximately 2 indicates that renal excretion of potassium is abnormally low for the prevailing hyperkalemia. Therefore, the inappropriately low TTKG indicates that the hyperkalemia is of renal tubular origin.

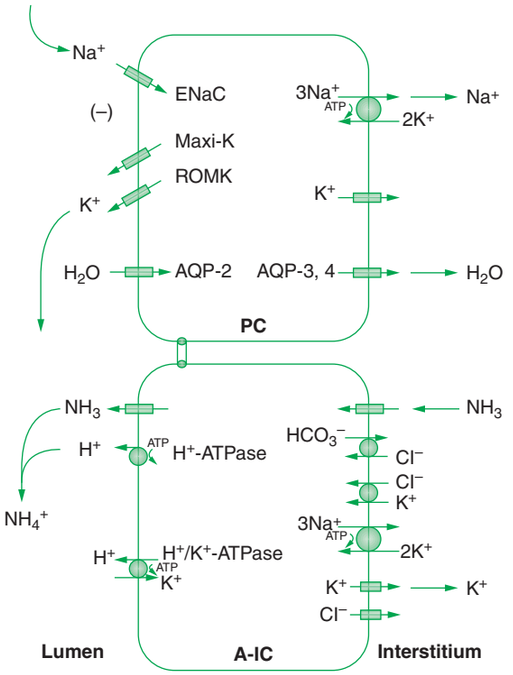

Figure e15-1 Water, sodium, potassium, ammonia, and proton transport in principal cells (PC) and adjacent type A intercalated cells. Water is absorbed down the osmotic gradient by principal cells through the apical aquaporin-2 (AQP-2) and basolateral aquaporin-3 and aquaporin-4 channels. The absorption of Na^+ via the amiloride-sensitive epithelial sodium channel (ENaC) generates a lumen-negative potential difference that drives K^+ excretion through the apical secretory K^+ channel, ROMK (renal outer medullary K^+ channel), and/or the flow-dependent maxi-K channel. Transepithelial ammonia (NH_3) transport and proton transport occur in adjacent type A intercalated cells via apical and basolateral ammonia channels and apical H^+-ATPase pumps, respectively; NH_4^+ ultimately is excreted in the urine in the defense of systemic pH. Electrogenic proton secretion by type A intercalated cells also is affected by the lumen-negative potential difference generated by the adjacent principal cells so that reduction of this lumen-negative electrical gradient can reduce H^+ excretion. Type A intercalated cells also reabsorb filtered K^+ in potassium-deficient states via apical H^+/K^+-ATPase.

APPROACH TO MANAGEMENT

Knowledge of the factors that control potassium secretion by the cortical collecting tubule principal cell can be helpful in understanding the basis for treatment of the hyperkalemia, especially if discontinuing the offending agent is not a reasonable clinical option. Potassium secretion is encouraged by a higher urine flow rate, increased distal delivery of sodium, distal delivery of a poorly reabsorbed anion (such as bicarbonate), and/or administration of a loop diuretic. Therefore, the approach to treatment in this patient should include intravenous 0.9% NaCl to expand the ECF and deliver more Na^+ and Cl^- to the cortical collecting tubule. In addition, as the TMP molecule must be protonated to inhibit ENaC, alkalinization of the renal tubule blunts the effect of the drug on distal tubular K^+ secretion. As an alternative to inducing bicarbonaturia to assist in potassium secretion, a carbonic anhydrase inhibitor could be administered to induce a significant kaliuresis. However, in the case presented here, for acetazolamide to be effective, the non-anion-gap metabolic acidosis in this patient would have to be corrected first; acetazolamide thus would require the coadministration of intravenous sodium bicarbonate for maximal benefit. Finally, systemic hyperkalemia directly suppresses renal ammoniagenesis, ammonium excretion, and thus acid excretion. Correcting the hyperkalemia with a potassium-binding resin (Kayexalate) sometimes is appropriate in these patients; the subsequent decline in the plasma K^+ concentration also will increase urinary ammonium excretion, helping to correct the acidosis.

CASE 3

A 63-year-old man was admitted to the intensive care unit (ICU) with a severe aspiration pneumonia. Past medical history included schizophrenia for which he required institutional care; treatment had included neuroleptics and intermittent lithium, with the lithium restarted 6 months before admission. The patient was treated with antibiotics and intubated for several days, with the development of polyuria (3–5 L/d), hypernatremia, and acute renal insufficiency; the peak plasma Na^+ concentration was 156 meq/L, and peak creatinine was 2.6 mg/dL. Urine osmolality was measured once and reported as 157 mosmol/kg, with a coincident plasma osmolality of 318 mosmol/kg. Lithium was stopped on admission to the ICU.

On physical examination, the patient was alert, extubated, and thirsty. Weight was 97.5 kg. Urine output for the last 24 h had been 3.4 L, with an IV intake of 2 L/d of D_5W.

Laboratory Data

Na^+ 150	K^+ 3.9	Cl^- 114	HCO_3^- 26	BUN 8	Creat 1.7
Glu 95	Alb 3.1	Ca^{2+} 8.1	Phos 2.6	Mg 2	Plasma osm 315
Urine:	Na^+ 34	K^+ 5.2	Osm 137		

After 3 days of intravenous hydration, a water deprivation test was performed. A single dose of 2 μg IV desmospressin (DDAVP) was given at 9 h (+9):

Laboratory Data

Time (h)	0	+6	+8	+12	+18
Na^+	145	148	150	152	149
K^+	5.4	5.3	3.9	3.9	3.9
Cl^-	111	110	118	120	114
HCO_3^-	24	27	25	242	25
Creat	1.3	1.3	1.4	1.3	1.3
S_{osmol}	300	311	315		
U_{osmol}	132	140	201	237	257
AVP		8.4	6.3		

APPROACH TO DIAGNOSIS

Why did the patient develop hypernatremia, polyuria, and acute renal insufficiency? What does the water deprivation test demonstrate? What is the underlying pathophysiology of this patient's hypernatremic syndrome?

This patient became polyuric after admission to the ICU with severe pneumonia and developed significant hypernatremia and acute renal insufficiency. Polyuria can result from either an osmotic diuresis or a water diuresis. An osmotic diuresis can be caused by excessive excretion of Na^+-Cl^-, mannitol, glucose, and/or urea, with a daily solute excretion of >750–1000 mosmol/d (>15 mosmol/kg body water per day). In this case, however, the patient was excreting large volumes of very hypotonic urine, with a urine osmolality that was substantially lower than that of plasma; this, by definition, was a water diuresis, resulting in inappropriate excretion of free water and hypernatremia. The appropriate response to hypernatremia and a plasma osmolality >295 mosmol/kg is an increase in circulating vasopressin (AVP) and the excretion of low volumes (<500 mL/d) of maximally concentrated urine, i.e., urine with osmolality >800 mosmol/kg; this patient's response to hypernatremia was clearly inappropriate, due to either a loss of circulating AVP [central

diabetes insipidus (CDI)] or renal resistance to AVP [nephrogenic diabetes insipidus (NDI)]. Ongoing loss of free water was sufficiently severe that absolute hypovolemia ensued despite the fact that approximately two-thirds of the excreted water was derived from the intracellular fluid (ICF) compartment rather than the ECF compartment. Hypovolemia led to an acute decrease in glomerular filtration rate (GFR), i.e., acute renal insufficiency, with gradual improvement following hydration (see below).

After correction of the hypernatremia and acute renal insufficiency with appropriate hydration (see below), the patient was subjected to a water deprivation test followed by administration of DDAVP. This test helps determine whether an inappropriate water diuresis is caused by CDI or NDI. The patient was water-restricted beginning in the early morning, with careful monitoring of vital signs and urine output; overnight water deprivation of patients with diabetes insipidus is unsafe and clinically inappropriate because of the potential for severe hypernatremia. The plasma Na^+ concentration—more accurate and more immediately available than plasma osmolality—was monitored hourly during water deprivation. A baseline AVP sample was drawn at the beginning of the test, with a second sample drawn once the plasma Na^+ reached 148–150 meq/L. At this point a single 2-μg dose of the V2 vasopressin receptor agonist DDAVP was administered. An alternative approach would have been to measure AVP and administer DDAVP when the patient was initially hypernatremic; however, it would have been less safe to administer DDAVP in the setting of renal impairment as clearance of DDAVP is renal-dependent.

The patient's water deprivation test was consistent with NDI, with an AVP level within the normal range in the setting of hypernatremia (i.e., no evidence of CDI) and an inappropriately low urine osmolality that failed to increase by >50%, or >150 mosmol/kg, after both water deprivation and the administration of DDAVP. This defect would be considered compatible with "complete" NDI; patients with "partial NDI" can achieve urine osmolalities of 500–600 mosmol/kg after DDAVP treatment but will not concentrate their urine maximally to 800 mosmol/kg or higher.

NDI has a number of genetic and acquired causes, which all share interference with some aspect of the renal concentrating mechanism. For example, loss-of-function mutations in the V2 AVP receptor cause X-linked NDI. This patient had NDI due to lithium therapy, perhaps the most common cause of NDI in adults. Lithium causes NDI via direct inhibition of renal glycogen synthase kinase-3 (GSK3), a kinase thought to be the pharmacologic target of lithium in psychiatric disease; renal GSK3 is required for the response of principal cells to AVP. Lithium also induces the expression of cyclooxygenase 2 (COX-2) in the renal medulla; COX-2-derived prostaglandins inhibit AVP-stimulated salt transport by the thick ascending limb and AVP-stimulated water transport by the collecting duct, exacerbating lithium-associated polyuria. The entry of lithium through the amiloride-sensitive Na^+ channel ENaC (Fig. e15-1) is required for the effect of the drug on principal cells, and so combined therapy with lithium and amiloride can mitigate lithium-associated NDI. However, lithium causes chronic tubulointerstitial scarring and chronic kidney disease after prolonged therapy so that patients may have a persistent NDI long after stopping the drug, with a reduced therapeutic benefit from amiloride. Notably, this patient had been treated intermittently for several years with lithium, with the development of chronic kidney disease (baseline creatinine 1.3–1.4) and NDI that persisted after the drug was stopped.

APPROACH TO MANAGEMENT

How should this patient have been 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 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 a 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 so that plasma Na^+ concentration either fails to correct or, in fact, increases.

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

$$C_eH_2O = V\left(1 - \frac{U_{Na} + U_K}{P_{Na}}\right)$$

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

For this particular 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 utilized 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 for 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 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 earlier 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 that was 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:

Laboratory Data

Na^+ 120	K^+ 4.3	Cl^- 89	HCO_3^- 23	BUN 8	Creat 1	Glu 93
Alb 3.1	Ca^{2+} 8.9	Phos 2.8	Mg 2	Plasma osm 248 mosmol/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

the 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 post-obstructive 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; those malignancies were not considered contributory to the 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 have a plasma Na^+ concentration <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, *myo*-inositol, 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 a 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 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, in which it can take weeks to months for a tissue diagnosis and the subsequent reduction in AVP after the 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 utilized to estimate electrolyte-free water excretion and the required degree of water restriction; patients with a ratio >1 should be restricted more aggressively (<500 mL/d), those with a ratio ~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/day. A more aggressive water restriction theoretically would have been successful; however, this can be very difficult for patients with SIAD to tolerate because their thirst is also inappropriately stimulated.

Combined therapy with furosemide and salt tablets often can increase the plasma Na^+ concentration in SIAD; furosemide reduces maximal urinary concentrating ability by inhibiting the countercurrent mechanism, and the salt tablets mitigate diuretic-associated NaCl loss. This regimen is not always successful and requires careful titration of salt tablets to avoid volume depletion; indeed, in this patient the plasma Na^+ concentration remained <130 meq/L, and the patient became orthostatic. The principal cell toxin, demeclocycline, is an alternative oral agent for 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 also has been implicated in nephrotoxic injury, particularly in patients with cirrhosis and chronic liver disease, in whom the drug accumulates. Notably, this 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 vasopressin antagonists (vaptans). These agents inhibit the effect of AVP on renal V2 receptors, resulting in the excretion of electrolyte-free water and correction of hyponatremia. The specific indications for these agents are not 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 play 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 V2-specific oral vaptan) would have been the next appropriate step in light of the development of renal insufficiency with demeclocycline. As with other measures to correct hyponatremia (hypertonic saline, demeclocycline, etc.) 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 as well.

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, and headache. Past medical history included hypertension, kidney stones, and hypercholesterolemia; medications included atenolol, spironolactone, and lovastatin. She also reliably consumed >2 L of liquid a day in management of 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 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 e15-1). 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) 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 e15-1.

TABLE e15–1 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
Creat (mg/dL)	1.2	2.35	2.10	2.02	1.97	1.79	1.53	1.20	1.13
Urine osmolality (mosmol/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 1 L 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 1 L 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 d of acute exacerbation. This patient was judged to have "chronic" hyponatremia, i.e., with a suspected duration >48 h; as such, she would be predisposed to osmotic demyelination if she underwent too rapid a correction in her plasma Na^+ concentration, i.e., by more than 8–10 meq/L in 24 h or 18 meq/L in 48 h. At presentation, she had no symptoms that one typically would attribute to acute hyponatremia, and the plasma Na^+ concentration already had increased by a sufficient amount to protect her from cerebral edema; however, she had corrected by 1 meq/L per h 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. In light of 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 e15-1).

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 "relowering" plasma Na^+ concentration with DDAVP and free water administration; this approach is demonstrably safe in patients with hyponatremia, with no evident risk of a seizure or other sequelae. This combination can be used to prevent an overcorrection or to relower plasma Na^+ concentration in patients who already have overcorrected. DDAVP is required, since 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 because of the relative absence of circulating AVP.

This patient's plasma Na^+ concentration remained depressed for several days after DDAVP administration. It is conceivable that residual hypovolemic hyponatremia attenuated the recovery of the plasma Na^+ concentration. Alternatively, attenuated recovery was due to persistent effects of the single dose of DDAVP. Of note, although the plasma half-life of DDAVP is only 1–2 h, pharmacodynamic studies indicate a much more prolonged effect on urine output and/or urine osmolality. A final consideration is the effect of the patient's initial renal dysfunction on the pharmacokinetics and pharmacodynamics of the administered DDAVP, which is excreted renally; DDAVP should be administered with caution for the reinduction of hyponatremia in patients with chronic kidney disease or acute renal dysfunction.

CASE 6

A 44-year-old woman was referred from a local hospital after presenting with flaccid paralysis. Severe hypokalemia was documented (2.0 meq/L), and an infusion containing KCl was initiated.

Laboratory Data	Value	Units
Na^+	140	meq/L
K^+	2.6	meq/L
Cl^-	115	meq/L
Bicarbonate	15	meq/L
Anion gap	10	meq/L
BUN	22	mg/dL
Creat	1.4	mg/dL
Arterial Blood Gases		
pH	7.32	U
Pa_{CO_2}	30	mmHg
HCO_3^-	15	meq/L

Additional laboratory data were rheumatoid factor–positive, anti-Ro/SS-A–, and anti-La/SS-B–positive. Urinalysis revealed a pH of 6.0, normal sediment without white or red blood cell casts, and no bacteria. The ratio of urine protein to creatinine was 0.150 g/g. Urinary electrolyte values were Na^+ 35, K^+ 40, Cl^- 18 meq/L. Therefore, the urine anion gap was positive, indicating low urine NH_4^+ excretion.

APPROACH TO DIAGNOSIS

The most accurate diagnosis in this case is classic hypokalemic distal renal tubular acidosis from Sjögren's syndrome. This patient presented with a non-anion-gap metabolic acidosis. The urine anion gap was positive, indicating an abnormally low excretion of ammonium in the face of systemic acidosis. The urine pH was inappropriately alkaline, yet there was no evidence of hypercalciuria, nephrocalcinosis, or bone disease. The patient subsequently was shown to exhibit hyperglobulinemia. These findings, taken together, indicate that the cause of this patient's hypokalemia and non-anion-gap metabolic acidosis was a renal tubular abnormality. The hypokalemia and abnormally low excretion of ammonium, as estimated by the urine anion gap, in the absence of glycosuria, phosphaturia, or aminoaciduria (Fanconi syndrome), defines the entity classical distal renal tubular acidosis (dRTA), also known as type 1 RTA. Because of the hyperglobulinemia, additional serology was obtained, providing evidence for the diagnosis of primary Sjögren's

syndrome. Furthermore, additional history indicated a 5-year history of xerostomia and keratoconjunctivitis sicca but without synovitis, arthritis, or rash.

Classical dRTA occurs frequently in patients with Sjögren's syndrome and is a result of an immunologic attack on the collecting tubule, causing failure of H^+-ATPase in the type A intercalated cell. Sjögren's syndrome is one of the best documented acquired causes of classical dRTA. The loss of H^+-ATPase function also occurs with certain inherited forms of classical dRTA. There was no family history in this case, and other family members were not affected. A number of autoantibodies have been associated with Sjögren's syndrome; it is likely that those autoantibodies prevent trafficking or function of the H^+-ATPase in the type A intercalated cell of the collecting tubule. Although proximal RTA has also been reported in patients with Sjögren's syndrome, it is much less common, and there were no features of proximal tubule dysfunction (Fanconi syndrome) in this patient. The hypokalemia is due to secondary hyperaldosteronism from volume depletion.

APPROACH TO MANAGEMENT

The long-term renal prognosis for patients with classic dRTA due to Sjögren's syndrome has not been established. Nevertheless, the metabolic acidosis and the hypokalemia respond to alkali replacement with either sodium citrate solution (Shohl's solution) or sodium bicarbonate tablets. Obviously, potassium deficits must be replaced initially, but potassium replacement usually is not required in a dRTA patient over the long term because sodium bicarbonate (or citrate) therapy expands volume and corrects the secondary hyperaldosteronism. A consequence of the interstitial infiltrate seen in patients with Sjögren's syndrome and classic dRTA is progression of chronic kidney disease. Cytotoxic therapy plus glucocorticoids has been the mainstay of therapy in Sjögren's syndrome for many years, although infiltration of B lymphocytes in salivary gland tissue subsides and urinary acidification improves after treatment with rituximab.

CASE 7

A 32-year-old man was admitted to the hospital with weakness and hypokalemia. The patient had been very healthy until 2 months previously, when he developed intermittent leg weakness. His review of systems was otherwise negative. He denied drug or laxative abuse and was on no medications. Past medical history was unremarkable, with no history of neuromuscular disease. Family history was notable for a sister with thyroid disease. Physical examination was notable only for reduced deep tendon reflexes.

Laboratory Data	Admission	Baseline	Units
Na^+	139	143	meq/L
K^+	2.0	3.8	meq/L
Cl^-	105	107	meq/L
Bicarbonate	26	29	meq/L
BUN	11	16	mg/dL
Creat	0.6	1.0	mg/dL
Ca^{2+}	8.8	8.8	mg/dL
Phosphate	1.2		mg/dL
Albumin	3.8		mg/dL
Plasma osmolality	290		mosmol/kg
Urine osmolality	590		mosmol/kg
Urine K^+	10		meq/L
TSH 0.08 μIU/L (normal 0.2–5.39)			
Free T_4 41 pmol/L (normal 10–27)			

APPROACH TO DIAGNOSIS

This patient developed hypokalemia due to a redistribution of potassium between the intracellular and extracellular compartments; this pathophysiology was readily apparent after calculation of the transtubular potassium gradient. The TTKG is calculated as $(P_{osmol} \times U_{Potassium})/(P_{Potassium} \times U_{osmol})$. The expected values for TTKG are <3 in the presence of hypokalemia and >7–8 in the presence of hyperkalemia (see Case 2 and Case 8). In this case the calculated TTKG was 2.5, consistent with appropriate renal conservation of K^+ and a nonrenal cause for hypokalemia. In the absence of significant gastrointestinal loss of K^+, the patient was diagnosed with a "redistributive" subtype of hypokalemia.

More than 98% of total-body potassium is intracellular; regulated buffering of extracellular K^+ by this large intracellular pool plays a crucial role in the maintenance of a stable plasma K^+ concentration. Clinically, changes in the exchange and distribution of intra- and extracellular K^+ can cause significant hypo- or hyperkalemia. Insulin, β_2-adrenergic activity, thyroid hormone, and alkalosis promote cellular uptake of K^+ by multiple interrelated mechanisms, leading to hypokalemia. In particular, alterations in the activity of the endogenous sympathetic nervous system can cause hypokalemia in several settings, including alcohol withdrawal, hyperthyroidism, acute myocardial infarction, and severe head injury.

Weakness is common in severe hypokalemia; hypokalemia causes hyperpolarization of muscle, impairing the capacity to depolarize and contract. In this patient, Graves' disease caused hyperthyroidism and hypokalemic paralysis [thyrotoxic periodic paralysis (TPP)]. TPP develops more frequently in patients of Asian or Hispanic origin. This predisposition has been linked to genetic variation in Kir2.6, a muscle-specific thyroid hormone–induced K^+ channel; however, the pathophysiologic mechanisms that link dysfunction of this ion channel to TPP have not been elucidated. The hypokalemia in TPP is attributed to both direct and indirect activation of Na^+, K^+-ATPase by thyroid hormone, resulting in increased uptake of K^+ by muscle and other tissues. Thyroid hormone induces expression of multiple subunits of Na^+, K^+-ATPase in skeletal muscle, increasing the capacity for uptake of K^+; hyperthyroid increases in β-adrenergic activity are also thought to play an important role in TPP.

Clinically, patients with TPP present with weakness of the extremities and limb girdle, with paralytic episodes that occur most frequently between 1 and 6 A.M. Precipitants of weakness include high carbohydrate loads and strenuous exercise. Signs and symptoms of hyperthyroidism are not always present, often leading to delays in diagnosis. Hypokalemia is often profound and usually is accompanied by redistributive hypophosphatemia, as in this case. A TTKG <2–3 separates patients with TPP from those with hypokalemia due to renal potassium wasting, who have TTKG values >4. This distinction is of considerable importance for therapy; patients with large potassium deficits require aggressive repletion with K^+-Cl^-, which confers a significant risk of rebound hyperkalemia in TPP and related disorders.

APPROACH TO MANAGEMENT

Ultimately, definitive therapy for TPP requires treatment of the associated hyperthyroidism. In the short term, however, potassium replacement is necessary to hasten muscle recovery and prevent cardiac arrhythmias. The average recovery time for an acute attack is reduced by ~50% in patients treated with intravenous K^+-Cl^- at a rate of 10 meq/h; however, this incurs a significant risk of rebound hyperkalemia, with up to 70% developing a plasma K^+ concentration >5.0 meq/L. This potential for rebound hyperkalemia is a general problem in the management of all causes of "redistributive

hypokalemia," resulting in the need to distinguish these patients accurately and rapidly from those with a large K^+ deficit due to renal or extrarenal loss of K^+. An attractive alternative to K^+-Cl^- replacement in TPP is treatment with high-dose propranolol (3 mg/kg), which rapidly reverses the associated hypokalemia, hypophosphatemia, and paralysis. Notably, rebound hyperkalemia is not associated with this treatment.

CASE 8

A 66-year-old man was admitted to the hospital with a plasma K^+ concentration of 1.7 meq/L and profound weakness. The patient had noted progressive weakness over several days, to the point where he was unable to rise from bed. Past medical history was notable for small cell lung cancer with metastases to brain, liver, and adrenals. The patient had been treated with one cycle of cisplatin/etoposide 1 year before this admission, complicated by acute kidney injury (peak creatinine of 5 mg/dL, with residual chronic kidney disease), and three subsequent cycles of cyclophosphamide/doxorubicin/vincristine, in addition to 15 treatments with whole-brain radiation.

On physical examination the patient was jaundiced. Blood pressure (bp) was 130/70, increasing to 160/98 after 1 L of saline, with a JVP of 8 cm. There was generalized muscle weakness.

Laboratory Data	2 Months PTA	Admission	HD2	Units
Na^+	143	149	144	meq/L
K^+	3.7	1.7	3.5	meq/L
Cl^-	103	84	96	meq/L
Bicarbonate	26	44	34	meq/L
Venous pH		7.47		pH
Venous P_{CO_2}		62		mm Hg
BUN	21	41	40	mg/dL
Creat	2.8	2.9	2.3	mg/dL
Mg^{2+}	1.3	1.6	2.4	mg/dL
CPK		183		U/L
ALT	8	75		U/L
Albumin	3.4	2.8	2.3	
Adjusted anion gap	15	24	18	
Total bilirubin	0.65	5.19		mg/dL
Alkaline phosphatase	93	217		U/L
Urine Na^+		35	28	meq/L
Urine K^+		25	49	meq/L
Urine chloride		48	51	meq/L
Urine osmolality		391		mosmol/kg
Plasma osmolality		312		mosmol/kg
Urine pH		5.5		
Plasma ACTH		185	pg/mL (7–50 pg/mL)	
Plasma cortisol		94	pg/mL (3–16 pg/mL)	
24-h Urine cortisol		1044	µg/24 h (4–50 µg/24 h)	

The patient's hospital course was complicated by acute respiratory failure attributed to pulmonary embolism; he died 2 weeks after admission.

APPROACH TO DIAGNOSIS

Why was this patient hypokalemic? Why was he weak? Why did he have an alkalosis?

This patient had metastatic small cell lung cancer that was persistent despite several rounds of chemotherapy and radiotherapy. He presented with profound hypokalemia, alkalosis, hypertension, severe weakness, jaundice, and worsening liver function tests.

With respect to the hypokalemia, there was no evident cause of nonrenal potassium loss, e.g., diarrhea. The urinary TTKG was 11.7, with a plasma K^+ concentration of 1.7 meq/L; this TTKG value is consistent with inappropriate renal K^+ secretion despite severe hypokalemia. The TTKG is calculated as $(P_{osmol} \times U_{Potassium})/(P_{Potassium} \times U_{osmol})$. The expected values for the TTKG are <3 in the presence of hypokalemia and >7–8 in the presence of hyperkalemia (see Case 2 and Case 6).

There were several explanations for the excessive renal loss of potassium. First, the patient had had a history of cisplatin-associated acute kidney injury with residual chronic kidney disease. Cisplatin can cause persistent renal tubular defects, with prominent hypokalemia and hypomagnesemia; however, this patient had not previously required potassium or magnesium repletion, suggesting that cisplatin-associated renal tubular defects did not play a major role in this presentation with severe hypokalemia. Second, he was hypomagnesemic on presentation, suggesting total-body magnesium depletion. Magnesium depletion has inhibitory effects on muscle Na^+,K^+-ATPase activity, reducing influx into muscle cells and causing a secondary increase in K^+ excretion. Magnesium depletion also increases K^+ secretion by the distal nephron; this is attributed to a reduction in the magnesium-dependent intracellular block of K^+ efflux through the secretory K^+ channel of principal cells [renal outer medullary K^+ channel (ROMK); Fig. e15-1]. Clinically, hypomagnesemic patients are refractory to K^+ replacement in the absence of Mg^{2+} repletion. Again, however, this patient had not previously developed significant hypokalemia despite periodic hypomagnesemia, and so other factors must have caused the severe hypokalemia.

The associated hypertension in this case suggested an increase in mineralocorticoid activity, causing increased activity of ENaC channels in principal cells, NaCl retention, hypertension, and hypokalemia. The increase an ENaC-mediated Na^+ transport in principal cells would have led to an increase in the lumen-negative potential difference in the connecting tubule and cortical collecting duct, driving an increase in K^+ secretion through apical K^+ channels (Fig. e15-1). This explanation is compatible with the very high TTKG, i.e., an increase in K^+ excretion that is inappropriate for the plasma K^+ concentration.

What caused an increase in mineralocorticoid activity in this patient? The patient had bilateral adrenal metastases, indicating that primary hyperaldosteronism was unlikely. The clinical presentation (hypokalemia, hypertension, and alkalosis) and the history of small cell lung cancer (SCLC) suggested Cushing's syndrome, with a massive increase in circulating glucocorticoids, in response to ectopic adrenocorticotropic hormone (ACTH) secretion by the SCLC tumor. Confirmation of this diagnosis was provided by a very high plasma cortisol level, high ACTH level, and increased urinary cortisol (see the laboratory data, above).

Why would an increase in circulating cortisol cause an apparent increase in mineralocorticoid activity? Cortisol and aldosterone have equal affinity for the mineralocorticoid receptor (MLR); thus, cortisol has "mineralocorticoid-like" activity. However, cells in the aldosterone-sensitive distal nephron [the distal convoluted tubule (DCT), connecting tubule (CNT), and collecting duct] are protected from circulating cortisol by the enzyme 11β-hydroxysteroid dehydrogenase-2 (11βHSD-2), which converts cortisol to cortisone (Fig. e15-2); cortisone has minimal affinity for the MLR. Activation of the mineralocorticoid receptor causes activation of the basolateral Na^+, K^+-ATPase, activation of the thiazide-sensitive Na^+-Cl^- co-transporter in the DCT, and activation of apical ENaC channels in principal cells of the CNT and collecting duct (Fig. e15-2). Recessive loss-of-function mutations in the *11βHSD-2* gene lead to cortisol-dependent activation of the MLR and the syndrome of apparent mineralocorticoid excess (SAME), which consists of

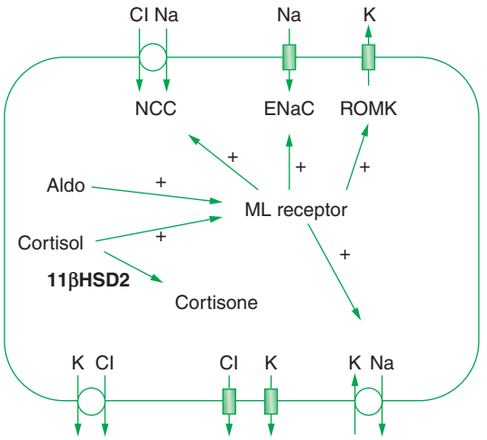

Figure e15-2 11β-Hydroxysteroid dehydrogenase-2 and syndromes of apparent mineralocorticoid excess. The enzyme 11β-hydroxysteroid dehydrogenase-2 (11βHSD-2) protects cells in the aldosterone-sensitive distal nephron [the distal convoluted tubule (DCT), connecting tubule (CNT), and collecting duct] from the illicit activation of mineralocorticoid receptors (MLR) by cortisol. Binding of aldosterone to the MLR leads to activation of the thiazide-sensitive Na^+-Cl^- co-transporter in DCT cells and the amiloride-sensitive epithelial sodium channel (ENaC) in principal cells (CNT and collecting duct). Aldosterone also activates basolateral Na^+, K^+-ATPase and, to a lesser extent, the apical secretory K^+ channel ROMK (renal outer medullary K^+ channel). Cortisol has equivalent affinity for the MLR to that of aldosterone; metabolism of cortisol to cortisone, which has *no* affinity for the MLR, prevents these cells from activation by circulating cortisol. Genetic deficiency of 11βHSD-2 or inhibition of its activity causes the syndromes of apparent mineralocorticoid excess (see Case 8).

hypertension, hypokalemia, hypercalciuria, and metabolic alkalosis, with suppressed plasma renin activity (PRA) and suppressed aldosterone. A similar syndrome is caused by biochemical inhibition of 11βHSD-2 by glycyrrhetinic/glycyrrhizinic acid (found in licorice, for example) and/or carbenoxolone.

In Cushing's syndrome caused by increases in pituitary ACTH, the incidence of hypokalemia is only 10%, whereas it is ~70% in patients with ectopic secretion of ACTH despite a similar incidence of hypertension. The activity of renal 11βHSD-2 is reduced in patients with ectopic ACTH compared with Cushing's syndrome, resulting in a syndrome of apparent mineralocorticoid excess; the prevailing theory is that the much greater cortisol production in ectopic ACTH syndromes overwhelms the renal 11βHSD-2 enzyme, resulting in activation of renal MLRs by unmetabolized cortisol (Fig. e15-2).

Why was the patient so weak? The patient was profoundly weak due to the combined effect of hypokalemia and increased cortisol. Hypokalemia causes hyperpolarization of muscle, impairing the capacity to depolarize and contract. Weakness and even ascending paralysis frequently can complicate severe hypokalemia. Hypokalemia also causes a myopathy and predisposes to rhabdomyolysis; notably, however, the patient had a normal creatine phosphokinase (CPK) level. Cushing's syndrome often is accompanied by a proximal myopathy due to the protein-wasting effects of cortisol excess.

The patient presented with a mixed acid-base disorder, with a significant metabolic alkalosis and a bicarbonate concentration of 44 meq/L. A venous blood gas was drawn soon after his presentation; venous and arterial blood gases demonstrate a high level of agreement in hemodynamically stable patients, allowing for the interpretation of acid-base disorders with venous blood gas results. In response to his metabolic alkalosis, the P_{CO_2} should have increased by 0.75 mmHg for each 1 meq/L increase in bicarbonate; the expected P_{CO_2} should have been ~55 mmHg. In light of the P_{CO_2} of 62 mmHg, he had an additional respiratory acidosis, probably caused by respiratory muscle weakness from the acute hypokalemia and subacute hypercortisolism.

The patient's albumin-adjusted anion gap was 21 + [(4–2.8) × 2.5] = 24; this suggests a third acid-base disorder: anion-gap acidosis. Notably, the measured anion gap can increase in alkalosis due to both increases in plasma protein concentrations (in hypovolemic alkalosis) and the alkalemia-associated increase in net negative charge of plasma proteins, with both causing an increase in "unmeasured anions." However, this patient was neither volume-depleted nor particularly alkalemic, suggesting that these effects played a minimal role in the increased anion gap. Alkalosis also stimulates an increase in lactic acid production due to activation of phosphofructokinase and accelerated glycolysis; unfortunately, however, a lactic acid level was not measured in this patient. It should be noted in this regard that alkalosis typically increases lactic acid levels by a mere 1.5–3 meq/L and that the patient was not significantly alkalemic. Regardless of the underlying pathophysiology, the increased anion gap probably was related to the metabolic alkalosis in light of the fact that the anion gap had decreased to 18 by hospital day 2, coincident with a reduction in plasma bicarbonate.

Why did the patient have a metabolic alkalosis? The activation of mineralocorticoid receptors in the distal nephron increases distal nephron acidification and net acid secretion. In consequence, mineralocorticoid excess causes a saline-resistant metabolic alkalosis, which is exacerbated significantly by the development of hypokalemia. Hypokalemia plays a key role in the generation of most forms of metabolic alkalosis, stimulating proximal tubular ammonium production, proximal tubular bicarbonate reabsorption, and distal tubular H^+,K^+-ATPase activity.

APPROACH TO MANAGEMENT

The first priority in the management of this patient was to increase his plasma K^+ and magnesium concentrations rapidly; hypomagnesemic patients are refractory to K^+ replacement alone, and there is a need to correct hypomagnesemia immediately. This was accomplished via the administration of both oral and intravenous K^+-Cl^-, giving a total of 240 meq over the first 18 h; 5 g of intravenous magnesium sulfate also was administered. Multiple 100-mL "minibags" of saline containing 20 meq each were infused, with cardiac monitoring and frequent measurement of plasma electrolytes. Of note, intravenous K^+-Cl^- should always be given in saline solutions, since dextrose-containing solutions can increase insulin levels and exacerbate hypokalemia.

This case illustrates the difficulty in predicting the whole-body deficit of K^+ in hypokalemic patients. In the absence of abnormal K^+ redistribution, the total deficit correlates with plasma K^+ concentration, which drops by approximately 0.27 m*M* for every 100-mmol reduction in total-body stores; this would suggest a deficit of ~650 meq of K^+ in this patient at the admission plasma K^+ concentration of 1.7 meq/L. Notably, however, alkalemia induces a modest intracellular shift of circulating K^+, and so this patient's initial plasma K^+ concentration was not an ideal indicator of the total potassium deficit. Regardless of the underlying pathophysiology in this case, close monitoring of plasma K^+ concentration is always essential during the correction of severe hypokalemia to gauge the adequacy of repletion and avoid overcorrection.

Subsequent management of this patient's Cushing's syndrome and ectopic ACTH secretion was complicated by the respiratory issues. The prognosis in patients with ectopic ACTH secretion depends on the tumor histology and the presence or absence of

distant metastases. This patient had an exceptionally poor prognosis with widely metastatic small cell lung cancer that had failed treatment; other patients with ectopic ACTH secretion caused by more benign, isolated tumors, most commonly bronchial carcinoid tumors, have a much better prognosis. In the absence of successful surgical resection of the causative tumor, management of this syndrome can include surgical adrenalectomy or medical therapy to block adrenal steroid production.

CASE 9

A stuporous 22-year-old man was admitted with a history of behaving strangely. His friends indicated he had experienced recent emotional problems stemming from a failed relationship and had threatened suicide. There was a history of alcohol abuse, but his friends were unaware of recent alcohol consumption. The patient was obtunded on admission, with no evident focal neurologic deficits. The remainder of the physical examination was unremarkable.

Laboratory data:

Na^+	140	meq/L
K^+	5	meq/L
Cl^-	95	meq/L
HCO_3^-	10	meq/L
Glucose	125	mg/dL
BUN	15	mg/dL
Creat	0.9	mg/dL
Ionized Ca^{2+}	4.0	mg/dL
Plasma osmolality	325	mosmol kg/H_2O

Urinalysis revealed crystalluria, with a mixture of envelope-shaped and needle-shaped crystals.

APPROACH TO DIAGNOSIS

This patient presented with CNS manifestations and a history of suspicious behavior, suggesting ingestion of a toxin. The anion gap was strikingly elevated at 35 meq/L. The ΔAG of 25 significantly exceeded the ΔHCO_3^- of 15. The fact that the delta values are significantly disparate indicates that the most likely acid-base diagnosis in this patient is a mixed high-anion-gap metabolic acidosis and a metabolic alkalosis. The metabolic alkalosis in this case may have been the result of vomiting. Nevertheless, the most useful finding is that the osmolar gap was elevated. The osmolar gap of 33 (difference in measured and calculated osmolality or 325–292) in the face of a high-gap metabolic acidosis is diagnostic of an osmotically active metabolite in plasma; a difference of >10 mosmol/kg indicates a significant concentration of an unmeasured osmolyte. Examples of toxic osmolytes include ethylene glycol, diethylene glycol, methanol, and propylene glycol.

Several caveats apply to the interpretation of the osmolar and anion gaps in the differential diagnosis of toxic alcohol ingestions. First, unmeasured, neutral osmolytes also can accumulate in lactic acidosis and alcoholic ketoacidosis; i.e., an elevated osmolar gap is not specific to anion-gap acidoses associated with toxic alcohol ingestions. Second, patients can present having extensively metabolized the ingested toxin, with an insignificant osmolar gap but a large anion gap; i.e., the absence of an elevated osmolar gap does not rule out toxic alcohol ingestion. Third, the converse can be seen in patients who present earlier after ingestion of the toxin, i.e., a large osmolar gap with minimal elevation of the anion gap. Finally, clinicians should be aware of the effect of coingested ethanol, which can itself elevate the osmolar gap and can reduce metabolism of the toxic alcohols via competitive inhibition of alcohol dehydrogenase (see below), thus attenuating the expected increase in the anion gap.

Ethylene glycol is commonly available as antifreeze or solvents and may be ingested accidentally or as a suicide attempt. The metabolism of ethylene glycol by alcohol dehydrogenase generates acids such as glycoaldehyde, glycolic acid, and oxalic acid. The initial effects of intoxication on the CNS in the earliest stages mimic inebriation but may quickly progress to full-blown coma. Delay in treatment is one of the most common causes of mortality with toxic alcohol poisoning. The kidney shows evidence of acute tubular injury with widespread deposition of calcium oxalate crystals within tubular epithelial cells. Cerebral edema is common, as is crystal deposition in the brain; the deposition is irreversible.

The co-occurrent crystalluria is typical of ethylene glycol intoxication; both needle-shaped monohydrate and envelope-shaped dihydrate calcium oxalate crystals can be seen in the urine as the process evolves. Circulating oxalate also can complex with plasma calcium, reducing the ionized calcium, as in this case.

Ethylene glycol intoxication should be verified by measuring ethylene glycol levels. However, therapy must be initiated immediately in this life-threatening situation. Although therapy can be initiated with confidence in cases with known or witnessed ingestions, such histories are rarely available. Therapy thus should be initiated in patients with severe metabolic acidosis and elevated anion and osmolar gaps. Other diagnostic features, such as hypocalcemia and acute renal failure with crystalluria, can provide important confirmation for urgent, empirical therapy.

APPROACH TO MANAGEMENT

Since all four osmotically active toxic alcohols—ethylene glycol, diethylene glycol, methanol, and propylene glycol—are metabolized by alcohol dehydrogenase to generate toxic products, competitive inhibition of this key enzyme is common to the treatment of all four intoxications. The most potent inhibitor of alcohol dehydrogenase, and the drug of choice in this circumstance, is fomepizole (4-methyl pyrazole). Fomepizole should be administered intravenously as a loading dose (15 mg/kg) followed by doses of 10 mg/kg every 12 h for four doses and then 15 mg/kg every 12 h thereafter until ethylene glycol levels have been reduced to <20 mg/dL and the patient is asymptomatic with a normal pH. Additional very important components of the treatment of toxic alcohol ingestion include fluid resuscitation, thiamine, pyridoxine, folate, sodium bicarbonate, and hemodialysis. Hemodialysis is used to remove both the parent compound and toxic metabolites but also removes administered fomepizole, necessitating adjustment of dose frequency. Gastric aspiration, induced emesis, or the use of activated charcoal is effective only if initiated within 30–60 min after ingestion of the toxin. When fomepizole is not available, ethanol, which has more than tenfold affinity for alcohol dehydrogenase compared with other alcohols, may be substituted and is quite effective. Ethanol must be administered IV to achieve a blood level of 22 meq/L (100 mg/dL). A disadvantage of ethanol is the obtundation that follows its administration, which is additive to the CNS effects of ethylene glycol. Furthermore, if hemodialysis is utilized, the infusion rate of ethanol must be increased because it is dialyzed rapidly. In general, hemodialysis is indicated for all patients with ethylene glycol intoxication when the arterial pH is <7.3 or the osmolar gap exceeds 20 mosmol/kg H_2O.

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