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 because 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^+ such that 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 in order to gauge the adequacy of repletion and to 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 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	Value	Units
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
Creatinine	0.9	mg/dL
Ionized calcium	4.0	mg/dL
Plasma osmolality	325	mOsm 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 AG was strikingly elevated at 35 meq/L. The ΔAG of 25 significantly exceeded the ΔHCO_3^- of 15. The fact that the Δ values were significantly disparate indicates that the most likely acid-base diagnosis in this patient is a mixed high-AG 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 is elevated. The osmolar gap of 33 (difference in measured and calculated osmolality or 325 – 292) in the face of a high-AG metabolic acidosis is diagnostic of an osmotically active metabolite in plasma; a difference of >10 mOsm/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 gap and AG in the differential diagnosis of toxic alcohol ingestions. First, unmeasured, neutral osmolytes can also accumulate in lactic acidosis and alcoholic ketoacidosis; i.e., an elevated osmolar gap is not specific to AG acidoses associated with toxic alcohol ingestions. Second, patients can present having extensively metabolized the ingested toxin, with an insignificant osmolar gap but a large AG; i.e., the absence of an elevated osmolar gap does not rule out toxic alcohol ingestion. Third, the converse can also be seen in patients who present earlier after ingestion of the toxin, i.e., a large osmolar gap with minimal elevation of the AG. Finally, clinicians should be aware of the effect of co-ingested 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 AG.

Ethylene glycol is commonly available as antifreeze or solvents and may be ingested accidently 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 are on the CNS and, 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 latter 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 can also complex with plasma calcium, reducing the ionized calcium as in this case.

Although ethylene glycol intoxication should be verified by measuring ethylene glycol levels, 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 should thus be initiated in patients with severe metabolic acidosis and elevated anion and osmolar gaps. Other diagnostic features, such as hypocalcemia or acute renal failure with crystalluria, can provide important confirmation for urgent, empiric therapy.

APPROACH TO MANAGEMENT

Because 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 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 it also removes administered fomepizole, necessitating adjustment of dosage frequency. Gastric aspiration, induced emesis, or the use of activated charcoal is only effective if initiated within 30–60 min after ingestion of the toxin. When fomepizole is not available, ethanol, which has more than 10-fold affinity for alcohol dehydrogenase compared to 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 used, the infusion rate of ethanol must be increased because it is rapidly dialyzed. 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 mOsm/kg H_2O.