Port J Nephrol Hypert 2017; 31(2): 73-78 • Advance Access publication 12 June 2017

Anion gap metabolic acidosis

Biff F. Palmer, M.D.[1], Deborah J. Clegg, Ph.D.[2]

[1] Department of Internal Medicine, University of Texas Southwestern Medical Center, Dallas, Texas
[2] Biomedical Research Department, Diabetes and Obesity Research Division, Cedars-Sinai Medical Center, Los Angeles, California

Received for publication: Jun 6, 2017
Accepted in revised form: Jun 12, 2017

Key words: anion gap, metabolic acidosis, lactic acidosis, ketoacidosis

INTRODUCTION

Metabolic acidosis is defined as a low arterial blood pH in conjunction with a reduced serum HCO_3^- concentration. Respiratory compensation results in a decrease in $PaCO_2$. A low serum HCO_3^- concentration alone is not diagnostic of metabolic acidosis because it also results from the renal compensation to chronic respiratory alkalosis. Measurement of the arterial pH differentiates between these two possibilities[1].

CALCULATION OF THE ANION GAP

After the diagnosis of metabolic acidosis is confirmed, the first step in the examination of metabolic acidosis is to calculate the serum anion gap. The anion gap is equal to the difference between the plasma concentrations of the major cation (Na^+) and the major measured anions (Cl^- and HCO_3^-) and is given by the following formula:

$$\text{Anion gap} = [Na^+] - ([Cl^-] + [HCO_3^-])$$

In healthy individuals, the normal value of the anion gap is approximately 12 mmol/l. Because many of the unmeasured anions consist of albumin, the normal anion gap is decreased by approximately 4 mmol/l for each 1 g/dl decrease in the serum albumin concentration below normal. The total number of cations must equal the total number of anions, so a decrease in the serum HCO_3^- concentration must be offset by an increase in the concentration of other anions[2]. If the anion accompanying excess H^+ is Cl^-, the decrease in the serum HCO_3^- concentration is matched by an equal increase in the serum Cl^- concentration. This acidosis is classified as a "normal anion gap" or a "non-anion gap" or a hyperchloremic metabolic acidosis. By contrast, if excess H^- is accompanied by an anion other than Cl^-, the decreased HCO_3^- is balanced by an increase in the concentration of the unmeasured anion. The Cl^- concentration remains the same. In this setting, the acidosis is said to be a "high anion gap" or "anion gap" metabolic acidosis.

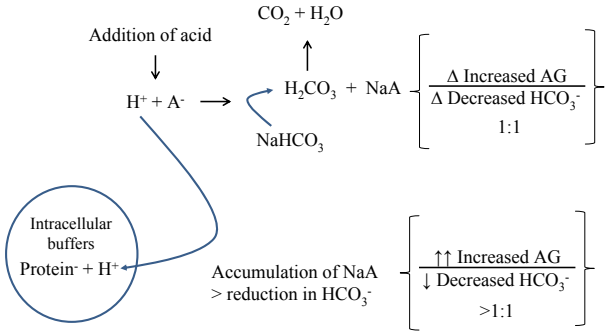
The normal value for the anion gap has tended to fall over time because of changes in how serum Na^+ and Cl^- are measured[3]. Flame photometry for Na^+ measurement and a colorimetric assay for Cl^- have been replaced by the use of ion-selective electrodes, with which the serum Na^+ values have largely remained the same, whereas the serum Cl^- values have tended to be higher. As a result, the normal value for the anion gap has decreased to as low as 6 mmol/l in some reports. Recognizing this change, some laboratories have adjusted the calibration set point for Cl^- to return the normal value for the anion gap to the 12 mmol/l range. It is important for the clinician to be aware that the average anion gap and range of normal values will vary among different facilities.

When the anion gap is increased one needs to determine whether the HCO_3^- is equal to the predicted value for HCO_3^-. In general, the HCO_3^- concentration will fall by an amount equal to the increase in anion gap. When the anion gap is greater than the fall in plasma HCO_3^- concentration, the presence of a metabolic alkalosis is suggested. One other

consideration is the amount of intracellular buffering that has occurred[4]. The reciprocal relationship between the change in anion gap and HCO_3^- concentration will be one for one if all buffering is confined to the extracellular space. With sufficient time, however, a large amount of H^+ becomes buffered outside of the extracellular space. To the extent that buffering has occurred in cells and bone, there will be no change in the plasma HCO_3^- concentration. As a result, acidosis of a more chronic nature will be associated with an increase in the anion gap that is greater than the fall in HCO_3^- concentration (Figure 1).

Figure 1

The immediate effect of an organic acid entering into the extracellular space is to metabolize HCO_3^- leading to an increased anion gap that is matched by an equivalent reduction in the plasma HCO_3^- concentration. With time intracellular buffering becomes more prominent so that buffering of the acid occurs without a reduction in plasma HCO_3^- concentration. At this time the increase in anion gap will be greater than the reduction in HCO_3^-.



When the decrease in HCO_3^- concentration is greater than what can be accounted for by an increase in anion gap, a coexisting normal (hyperchloremic) gap acidosis is suggested. This situation also occurs in anion gap acidosis when the acid anion is promptly excreted into the urine as a Na^+ or K^+ salt rather than with H^+ or NH_4^+. This indirect loss of HCO_3^- from the body will cause the anion gap to decrease without a concomitant increase in HCO_3^- concentration. This situation occurs in patients with normal renal function and ketoacidosis, toluene ingestion, or D-lactic acidosis[5].

ANION GAP METABOLIC ACIDOSIS

Lactic Acidosis

Lactic acid is the end product in the anaerobic metabolism of glucose and is generated by the reversible reduction of pyruvic acid by lactic acid dehydrogenase and NADH (reduced nicotinamide adenine dinucleotide), as shown in the following formula:

$$\text{pyruvate} + \text{NADH} + H^+ \leftrightarrow \text{lactate} + NAD^+$$

Under normal conditions, the reaction is shifted toward the right, and the normal lactate to pyruvate ratio is approximately 10:1. Lactate can accumulate for one of three reasons. First, lactate can increase as a consequence of increased pyruvate production alone. In this situation, the normal 10:1 lactate to pyruvate ratio will be maintained. An isolated increase in pyruvate production can be seen in the setting of intravenous glucose infusions, intravenous administration of epinephrine, and respiratory alkalosis. Lactate levels in these conditions are minimally elevated, rarely exceeding 5 mmol/l. Second, lactate can increase as a result of an increased NADH/NAD^+ ratio. Under these conditions, the lactate to pyruvate ratio can increase to very high values. Finally, lactate can increase when there is a combination of increased pyruvate production with an increased NADH/NAD^+ ratio. This latter condition is common in severe lactic acidosis[6].

Lactic acidosis occurs whenever there is an imbalance between the production and use of lactic acid. The net result is an accumulation of serum lactate and the development of metabolic acidosis. The accumulation of the non-chloride anion lactate accounts for the increase in anion gap. Severe exercise and grand mal seizures are examples of when lactic acidosis can develop as a result of increased production. The short-lived nature of the acidosis in these conditions suggests that a concomitant defect in lactic acid use is present in most conditions of sustained and severe lactic acidosis.

Type A lactic acidosis is characterized by under perfusion of tissue or acute hypoxia, such as hypotension, sepsis, acute tissue hypoperfusion, cardiopulmonary failure, severe anemia, hemorrhage, and carbon monoxide poisoning (Table 1). Type B lactic acidosis occurs in the absence of overt hypoperfusion or hypoxia, such as with congenital defects in glucose or lactate metabolism, diabetes mellitus, liver disease, effects of drugs and toxins, and neoplastic diseases. In clinical practice, many patients will often exhibit features of type A and type B lactic acidosis simultaneously.

Therapy is aimed at correction of the underlying disorder[7]. Restoration of tissue perfusion and

Table 1

Causes of lactic acidosis

- **Type A (tissue under perfusion and or hypoxia)**
  - Cardiogenic shock
  - Septic shock
  - Hemorrhagic shock
  - Acute hypoxia
  - Carbon monoxide poisoning
  - Anemia
- **Type B (absence of hypotension and hypoxia)**
  - Hereditary enzyme deficiency (glucose 6-phosphatase)
  - Drugs or toxins
    - phenformin, metformin,
    - cyanide
    - salicylate, ethylene glycol, methanol
  - Systemic disease
    - liver failure
    - malignancy

oxygenation is attempted if they are compromised. The role of alkali in the treatment of lactic acidosis is controversial; some experimental models and clinical observations suggest that administration of HCO_3^- may depress cardiac function and exacerbate the acidemia. In addition, such therapy may be complicated by volume overload, hypernatremia, and rebound alkalosis after the acidosis has resolved. In general, HCO_3^- should be given when the systemic pH decreases to below 7.1, as hemodynamic instability becomes much more likely with severe acidemia. In such cases, alkali therapy should be directed at increasing the pH above 7.1; attempts to normalize the pH or [HCO_3^-] should be avoided. Acute hemodialysis is rarely beneficial for lactic acidosis induced by tissue hypoperfusion. The hemodynamic instability that can occur with hemodialysis in these critically ill patients may worsen the underlying difficulty in tissue oxygenation.

■ Diabetic Ketoacidosis

Diabetic ketoacidosis results from the accumulation of acetoacetic acid and β-hydroxybutyric acid. The development of ketoacidosis is the result of insulin deficiency and a relative or absolute increase in glucagon[8]. These hormonal changes lead to increased fatty acid mobilization from adipose tissue and alter the oxidative machinery of the liver such that delivered fatty acids are primarily metabolized into keto acids. In addition, peripheral glucose use is impaired, and the gluconeogenic pathway in the liver is maximally stimulated. The resultant hyperglycemia causes an osmotic diuresis and volume depletion.

Ketoacidosis results when the rate of hepatic keto acid generation exceeds renal excretion, causing increased blood keto acid concentrations. The H^+ accumulation in the extracellular fluid decreases HCO_3^- concentration, whereas the keto acid anion concentration increases. An anion gap metabolic acidosis is the more common finding in diabetic ketoacidosis, but a normal gap metabolic acidosis can also be seen[9]. In early stages of ketoacidosis, when the extracellular volume is nearly normal, keto acid anions that are produced are rapidly excreted by the kidney as Na^+ and K^+ salts. Excretion of these salts is equivalent to the loss of potential HCO_3^-. This loss of potential HCO_3^- in the urine at the same time that the kidney is retaining NaCl results in a normal gap metabolic acidosis. As volume depletion develops, renal keto acid excretion cannot match production rates, and keto acid anions are retained within the body, thus increasing the anion gap.

During treatment, the anion gap metabolic acidosis transforms once again into a normal gap acidosis. Treatment leads to a termination in keto acid production. As the extracellular fluid volume is restored, there is increased renal excretion of the Na^+ salts of the keto acid anions. The loss of this potential HCO_3^- combined with the retention of administered NaCl accounts for the redevelopment of the hyperchloremic normal gap acidosis. In addition, K^+ and Na^+ administered in solutions containing NaCl and KCl enter cells in exchange for H^+. The net effect is infusion of HCl into the extracellular fluid. The reversal of the hyperchloremic acidosis takes several days as the HCO_3^- deficit is corrected by the kidney.

Diabetic ketoacidosis can result in a severe metabolic acidosis with serum bicarbonate levels below 5 mmol/l. This diagnosis should be considered in patients with simultaneous metabolic acidosis and hyperglycemia. Diagnosis is confirmed by demonstration of retained keto acids with nitroprusside tablets or reagent strips. However, these tests detect only acetone and acetoacetate and not β-hydroxybutyrate. In the setting of lactic acidosis or alcoholic ketoacidosis, acetoacetate may be converted to β-hydroxybutyrate to an extent that depends on the NADH/NAD^+ ratio. With treatment of the diabetic ketoacidosis, acetoacetate is generated as the NADH/NAD^+ ratio falls, and the nitroprusside test result may suddenly become strongly positive. The limitations of the nitroprusside test can be prevented by direct measurement of β-hydroxybutyrate. With uncontrolled diabetes, a serum β-hydroxybutyrate level above 3.0 and above 3.8 mmol/l in children and adults, respectively, confirms diabetic ketoacidosis. Compared

with urinary ketone measurements, capillary blood levels of β-hydroxybutyrate better correlate with both the degree of acidosis and the response to therapy.

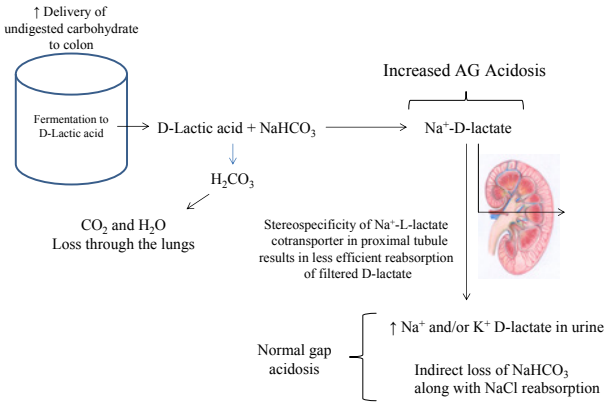
Treatment consists of insulin and intravenous fluids to correct volume depletion. Deficiencies in K^+, Mg^{2+}, and phosphate are common; therefore, these electrolytes are typically added to intravenous solutions. However, diabetic ketoacidosis typically presents with hyperkalemia due to the insulin deficiency[10-12]. Potassium should be administered only as hypokalemia develops, usually during insulin treatment of diabetic ketoacidosis. If there is significant hypokalemia at presentation, potassium supplementation may be needed before insulin administration to avoid life-threatening worsening of hypokalemia. Alkali therapy is generally not required because administration of insulin leads to the metabolic conversion of keto acid anions to HCO_3^- and allows partial correction of the acidosis. However, HCO_3^- therapy may be indicated in those patients who present with severe acidemia (pH < 7.1).

■ D-Lactic Acidosis

D-Lactic acidosis is a unique form of metabolic acidosis that can occur in the setting of small bowel resections or in patients with a jejunoileal bypass (Figure 2). Such short bowel syndromes create a situation in which carbohydrates that are normally extensively reabsorbed in the small intestine are delivered in large amounts to the colon[13]. In the presence of colonic bacterial overgrowth, these substrates are metabolized into d-lactate and absorbed into the systemic circulation. Accumulation of d-lactate produces an anion gap metabolic acidosis in which the serum lactate concentration is normal because the standard test for lactate is specific for l-lactate. These patients typically present after ingestion of a large carbohydrate meal with neurologic abnormalities consisting of confusion, slurred speech, and ataxia. Ingestion of low-carbohydrate meals and antimicrobial agents to decrease the degree of bacterial overgrowth are the principal treatments.

Figure 2

D-lactic acidosis can present with an increased and/or normal gap acidosis. D-lactate is more readily excreted by the kidney as compared to L-lactate leading to indirect loss of HCO_3^- from the body accounting for the development of a normal gap acidosis.



■ Starvation Ketosis

Abstinence from food can lead to a mild anion gap metabolic acidosis secondary to increased production of keto acids. The pathogenesis of this disorder is similar to that of diabetic ketoacidosis in that starvation leads to relative insulin deficiency and glucagon excess. As a result, there is increased mobilization of fatty acids while the liver is set to oxidize fatty acids to keto acids. With prolonged starvation, the blood keto acid level can reach 5 to 6 mmol/l. The serum [HCO_3^-] is rarely less than 18 mmol/l. More fulminant ketoacidosis is aborted by the fact that ketone bodies stimulate the pancreatic islets to release insulin and lipolysis is held in check[14]. This break in the ketogenic process is notably absent in those with insulin-dependent diabetes. There is no specific therapy indicated in this disorder.

■ Alcoholic Ketoacidosis

Ketoacidosis develops in patients with a history of chronic ethanol abuse, decreased food intake, and often a history of nausea and vomiting. As with starvation ketosis, a decrease in the insulin to glucagon ratio leads to accelerated fatty acid mobilization and alters the enzymatic machinery of the liver to favor keto acid production. However, there are features unique to this disorder that differentiate it from simple starvation ketosis. First, the alcohol withdrawal combined with volume depletion and starvation markedly increases the levels of circulating catecholamines[15]. As a result, the peripheral mobilization of fatty acids is much greater than that typically found with starvation alone. This sometimes massive mobilization of fatty acids can lead to marked keto acid production and severe metabolic acidosis. Second, the metabolism of ethanol leads to accumulation of NADH. The increase in the NADH/NAD^+ ratio is reflected by a higher β-hydroxybutyrate to acetoacetate ratio. As mentioned previously, the

nitroprusside reaction may be diminished by this redox shift despite the presence of severe ketoacidosis. Treatment of this disorder is focused on glucose administration, which leads to the rapid resolution of the acidosis because stimulation of insulin release leads to diminished fatty acid mobilization from adipose tissue as well as decreased hepatic output of keto acids.

■ Ethylene Glycol and Methanol Intoxications

Ethylene glycol and methanol intoxications are characteristically associated with the development of a severe anion gap metabolic acidosis[16]. Metabolism of ethylene glycol by alcohol dehydrogenase generates various acids, including glycolic, oxalic, and formic acids. Ethylene glycol is present in antifreeze and solvents and is ingested by accident or as a suicide attempt. The initial effects of intoxication are neurologic and begin with drunkenness but can quickly progress to seizures and coma. If left untreated, cardiopulmonary symptoms such as tachypnea, noncardiogenic pulmonary edema, and cardiovascular collapse may appear. Twenty-four to 48 hours after ingestion, patients may develop flank pain and acute kidney injury often accompanied by abundant calcium oxalate crystals in the urine. A fatal dose is approximately 100 ml.

Methanol is also metabolized by alcohol dehydrogenase and forms formaldehyde, which is then converted to formic acid. Methanol is found in a variety of commercial preparations, such as shellac, varnish, and deicing solutions, and is also known as wood alcohol. Like ethylene glycol, methanol can be ingested either by accident or as a suicide attempt. Clinically, methanol ingestion is associated with an acute inebriation followed by an asymptomatic period lasting 24 to 36 hours. Abdominal pain caused by pancreatitis, seizures, blindness, and coma may develop. The blindness is due to direct toxicity of formic acid on the retina. Methanol intoxication is also associated with hemorrhage in the white matter and putamen, which can lead to the delayed onset of a Parkinson's disease-like syndrome. The lethal dose is between 60 and 250 ml. Lactic acidosis is also a feature of methanol and ethylene glycol poisoning and contributes to the elevated anion gap.

Together with an elevated anion gap, an osmolar gap is an important clue to the diagnosis of ethylene glycol and methanol poisoning.

Calculated osmolality = 2 x $[Na^+]$(mEq/L) + BUN(mg/dl)/2.8 + Glucose(mg/dl)/18

The osmolar gap is the difference between the measured and calculated osmolality. The normal value for the osmolar gap is less than 10 mOsm/kg. Each 100 mg/dl (161 mmol/l) of ethylene glycol will increase the osmolar gap by 16 mOsm/kg; methanol contributes 32 mOsm/kg for each 100 mg/dl (312 mmol/l).

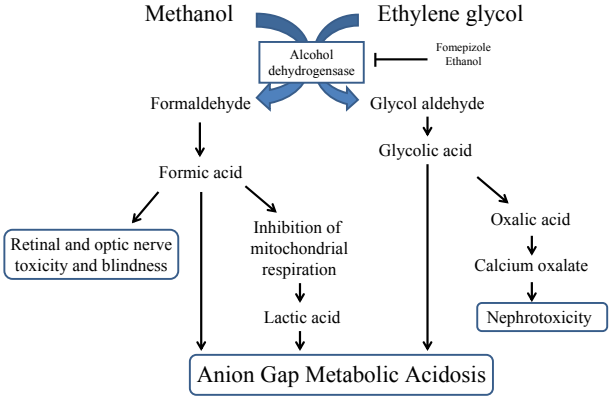
In addition to supportive measures, ethylene glycol and methanol poisoning are treated with fomepizole (4-methylpyrazole), which inhibits alcohol dehydrogenase and prevents formation of toxic metabolites (Figure 3). If fomepizole is unavailable, intravenous ethanol can be used to prevent the formation of toxic metabolites. Ethanol has more than a 10-fold greater affinity for alcohol dehydrogenase than that of other alcohols. Ethanol has its greatest efficacy when levels of 100 to 200 mg/dl are obtained. In addition to both fomepizole and ethanol therapy, hemodialysis should be employed to remove both the parent compound and its metabolites. Finally, correction of the acidosis is accomplished with use of an HCO_3^- containing dialysate or by intravenous infusion of $NaHCO_3$.

■ Salicylate

Aspirin (acetylsalicylic acid) is associated with a large number of accidental or intentional poisonings. At toxic concentrations, salicylate uncouples oxidative phosphorylation and, as a result, leads to increased lactic acid production. In children, keto acid production may also be increased. The accumulation of lactic, salicylic, keto, and other organic acids leads to the development of an anion gap metabolic acidosis[17]. At the same time, salicylate has a direct stimulatory effect on the

Figure 3

Metabolism and treatment of ethylene glycol and methanol.



respiratory center. Increased ventilation lowers the $PaCO_2$, contributing to the development of a respiratory alkalosis. Children primarily manifest an anion gap metabolic acidosis with toxic salicylate levels; a respiratory alkalosis is most evident in adults.

In addition to conservative management, the initial goals of therapy are to correct systemic acidemia and to increase the urine pH. By increasing systemic pH, the ionized fraction of salicylic acid will increase, and as a result, there will be less accumulation of the drug in the central nervous system. Similarly, an alkaline urine pH favors increased urinary excretion because the ionized fraction of the drug is poorly reabsorbed by the tubule. At serum concentrations above 80 mg/dl or in the setting of severe clinical toxicity, hemodialysis can be used to accelerate drug elimination.

■ Pyroglutamic Acidosis

Pyroglutamic acid, also known as 5-oxoproline, is an intermediate in glutathione metabolism. An anion gap acidosis due to pyroglutamic acid has been rarely described in critically ill patients receiving therapeutic doses of acetaminophen[18,19]. Affected patients present with severe anion gap metabolic acidosis accompanied by alterations in mental status ranging from confusion to coma. High concentrations of pyroglutamic acid are found in the blood and urine. In this setting, glutathione levels are reduced because of the oxidative stress associated with critical illness and by the metabolism of acetaminophen. The reduction in glutathione secondarily leads to increased production of pyroglutamic acid. The diagnosis of pyroglutamic acidosis should be considered in patients with unexplained anion gap metabolic acidosis and recent acetaminophen ingestion.

Disclosure of potential conflicts of interest: none declared

References

1. Palmer BF. Approach to fluid and electrolyte disorders and acid-base problems. Prim Care. 2008;35:195-213.
2. Emmett M, Narins RG. Clinical use of the anion gap. Medicine (Baltimore) 1977; 56:38-54
3. Kraut J, Madias N. Serum anion gap: Its uses and limitations in clinical medicine. Clin J Am Soc Nephrol. 2007;2:162-174.
4. Rastegar A. Use of the DeltaAG/DeltaHCO3- ratio in the diagnosis of mixed acid-base disorders. J Am Soc Nephrol 2007; 18:2429-2431.
5. Carlisle E, Donnelly S, Vasuvattakul S, Kamel K, Tobe S, Halperin M. Glue-sniffing and distal renal tubular acidosis: sticking to the facts. J Am Soc Nephrol. 1991;1(8):1019-27.
6. Kraut J, Madias N. Lactic acidosis. N Engl J Med. 2014;371(24):2309-19
7. Kraut J, Madias N. Lactic Acidosis: Current Treatments and Future Directions. Am J Kidney Dis. 2016;68(3):473-82
8. Foster DW, McGarry JD. The metabolic derangements and treatment of diabetic ketoacidosis. N Engl J Med. 1983;309:159-169.
9. Palmer BF, Clegg DJ. Electrolyte and Acid-Base Disturbances in Patients with Diabetes Mellitus. N Engl J Med. 2015;373:548-59
10. Palmer BF. A physiologic based approach to the evaluation of a patient with hyperkalemia. Am J Kidney Ds 2010;56(2):387-393
11. Palmer BF, Clegg DJ. Physiology and pathophysiology of potassium homeostasis. Adv Physiol Educ 2016; 40: 480-490
12. Palmer BF. Renal Physiology: Regulation of Potassium Homeostasis. Clin J Am Soc Nephrol 2015;10:1050-60
13. Uribarri J, Oh M, Carroll H. D-lactic acidosis. A review of clinical presentation, biochemical features, and pathophysiologic mechanisms. Medicine (Baltimore). 1998;77(2):73-82.
14. Palmer BF, Clegg DJ, Taylor SI, Weir MR. Diabetic ketoacidosis, sodium glucose transporter-2 inhibitors and the kidney. J Diabetes Complications. 2016;30:1162-6
15. Halperin ML, Hammeke M, Josse RG, Jungas RL. Metabolic acidosis in the alcoholic: a pathophysiologic approach. Metabolism 1983;32:308-15.
16. Kraut J, Kurtz I. Toxic alcohol ingestions: Clinical features, diagnosis, and management. Clin J Am Soc Nephrol. 2008;3:208-225.
17. Gabow P, Anderson R, Potts D, Schrier R. Acid-base disturbances in the salicylate-intoxicated adult. Arch Intern Med. 1978;138(10):1481-4.
18. Brooker G, Jeffery J, Nataraj T, et al. High anion gap metabolic acidosis secondary to pyroglutamic aciduria (5-oxoprolinuria): Association with prescription drugs and malnutrition. Ann Clin Biochem. 2007;44:406-409.
19. Fenves A, Kirkpatrick H, Patel V, et al. Increased anion gap metabolic acidosis as a result of 5-oxoproline (pyroglutamic acid): A role for acetaminophen. Clin J Am Soc Nephrol. 2006;1:441-447.

Correspondence to:
Biff F. Palmer, M.D.
Department of Internal Medicine
University of Texas Southwestern Medical Center
5323 Harry Hines Blvd.
Dallas, Texas 75390
biff.palmer@utsouthwestern.edu