Metabolic Acidosis

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ABSTRACT

Acute metabolic acidosis is frequently encountered in critically ill patients. Metabolic acidosis can occur as a result of either the accumulation of endogenous acids that consumes bicarbonate (high anion gap metabolic acidosis) or loss of bicarbonate from the gastrointestinal tract or the kidney (hyperchloremic or normal anion gap metabolic acidosis). The cause of high anion gap metabolic acidosis includes lactic acidosis, ketoacidosis, renal failure and intoxication with ethylene glycol, methanol, salicylate and less commonly with pyroglutamic acid (5-oxoproline), propylene glycol or djenkol bean (djenkolism). The most common causes of hyperchloremic metabolic acidosis are gastrointestinal bicarbonate loss, renal tubular acidosis, drugs-induced hyperkalemia, early renal failure and administration of acids. The appropriate treatment of acute metabolic acidosis, in particular organic form of acidosis such as lactic acidosis, has been very controversial. The only effective treatment for organic acidosis is cessation of acid production via improvement of tissue oxygenation. Treatment of acute organic acidosis with sodium bicarbonate failed to reduce the morbidity and mortality despite improvement in acid-base parameters. Further studies are required to determine the optimal treatment strategies for acute metabolic acidosis.

***Key words**: metabolic acidosis, high anion gap, hyperchloremic metabolic acidosis, sodium bicarbonate.*

INTRODUCTION

Metabolic acidosis (MA) is an acid-base disorder that is characterized by a fall in blood pH due to a reduction of serum bicarbonate concentration. This can occur as a result of either the accumulation of acids (high anion gap MA) or the loss of bicarbonate from the gastrointestinal tract or the kidney (hyperchloremic MA). Acid is present in two forms: volatile (e.g., carbonic) and nonvolatile (e.g., sulfuric, phosphoric) acids. On a typical diet, metabolism of sulfur-containing amino acids yields 20 to 40 mmol of nonvolatile sulfuric acid (H_2SO_4) daily and metabolism of phosphate esters generates the same amount of phosphoric acid. These acids dissociate into hydrogen ions, which are buffered by bicarbonate in the extracellular compartment. The phosphate anions are excreted in the urine as "titratable acid" and the sulfate anions as ammonium sulfate. The net result is a daily acid load in the range of 50-80 mEq of hydrogen ions.

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RENAL ACID HANDLING

To maintain normal pH, the kidneys have to perform two physiological functions. The first is to reabsorb all the filtered HCO_3^-, which occurs principally in the proximal tubule (PT). The second is to excrete the daily H^+ load, a function of the collecting duct (CD). The PT is responsible for reabsorbing approximately 80% of the filtered HCO_3^-. The thick ascending limb of Henle reabsorbs another 10% of filtered HCO_3^-, and the distal nephron the rest of HCO_3^-, so that virtually no HCO_3^- is left in the final urine.

The mechanisms for reabsorption of filtered HCO_3^- by PT are displayed in figure 1.[1] The PT reabsorbs HCO_3^- by secreting H^+ via an apical Na^+/H^+ exchanger (NHE-3) into the lumen. A small fraction of apical membrane H^+ secretion is mediated by an H^+-ATPase. The secreted H^+ reacts with filtered HCO_3^- to form luminal H_2CO_3, which quickly dissociates into CO_2 and H_2O by the membrane-bound carbonic anhydrase IV (CA IV). Luminal CO_2 can freely diffuse across the apical membrane via a bifunctional water/gas aquaporin 1 channel (AQP1).[2] Once inside the cell, CO_2 and H_2O recombine via cytoplasmic carbonic anhydrase II (CA II) to generate HCO_3^- and H^+. Bicarbonate generated within the cells exists across the basolateral membrane via a $Na^+/3HCO_3^-$ cotransporter (NBC-1).[3]

Excretion of the daily acid load (50-80 mEq of H^+) occurs principally through three mechanisms: free hydrogen ions excretion, titratable acidity and ammonium excretion. Urine pH cannot be lowered much below 5 because the gradient against which H^+-ATPase has to pump protons (intracellular pH 7.5 to luminal pH 5) becomes too steep. A maximally acidified urine, even

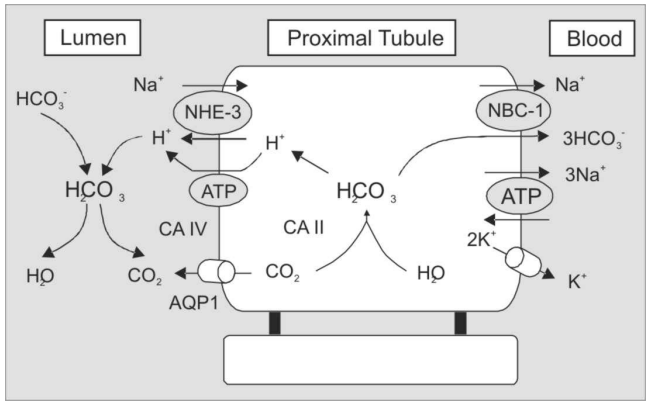

Figure 1. Model of HCO_3^- Reabsorption in The Proximal Tubule. The proximal tubule reabsorbs HCO_3^- by secreting H^+ via a specific Na^+/H^+ exchanger (NHE-3) into the lumen and titrating HCO_3^- to CO_2 and H_2O via a luminal membrane-bound carbonic anhydrase IV (CA IV). CO_2 diffuses across the apical membrane via a bifunctional water/gas aquaporin 1 channel (AQP1). Once inside the cell, CO_2 and H_2O recombine via cytoplasmic carbonic anhydrase II to generate HCO_3^-, which exists across the basolateral membrane via a $Na^+/3HCO_3^-$ cotransporter (NBC-1).

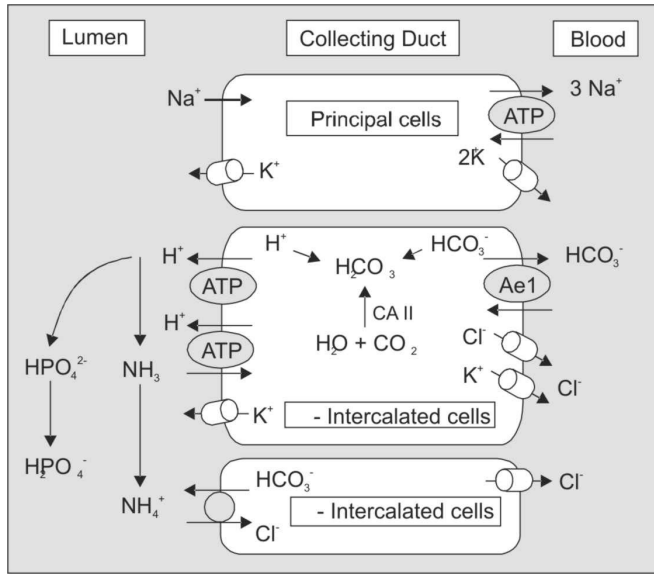

Figure 2. Model of H^+ Secretion in The Collecting Duct. The main pump for luminal H^+ secretion is an apical H^+-ATPase in the á-intercalated cell. A second ATPase, the H^+/K^+-ATPase, is also involved in H^+ secretion. Intracellularly formed HCO_3^- leaves the cell by an electroneutral mechanism involving a basolateral band 3-like Cl^-/HCO_3^- anion exchanger (AE1). Intercalated cells are very rich in cytoplasmic carbonic anhydrase II (CA II).

with a volume of 3 L, would thus contain a mere 0.03 mEq of free H^+. Hence, free H^+ excretion is an insignificant contribution to total urinary acid excretion. Therefore, the major daily H^+ excretion is through titratable acidity and renal ammonium production.

The amount of secreted H^+ that is buffered by filtered weak acids is called titratable acidity. The major filtered buffer is $HPO_4^{2-}/H_2PO_4^-$. The intercalated cells in the CD are responsible for both H^+ and HCO_3^- secretion, whereas the principal cells are in charge of Na^+ reabsorption and K^+ secretion. (Figure 2) The α-intercalated cell is responsible for secretion of H^+. The main pump for luminal H^+ secretion is an apical H^+-ATPase. A second ATPase, the H^+/K^+-ATPase, is also involved in H^+ secretion. The secreted luminal H^+ is able to titrate HPO_4^{2-} almost completely to $H_2PO_4^-$, which can account for excretion of 30-40 mEq H^+/day. The H^+ is derived from conversion of CO_2 and H_2O to H^+ and HCO_3^-, which is catalyzed by cytoplasmic CA II. Intracellularly formed HCO_3^- leaves the cell by an electroneutral mechanism involving a basolateral band 3-like Cl^-/HCO_3^- anion exchanger.[4] In contrast to phosphate anions, sulfate anions can not be excreted with H^+ because the pK of sulfuric acid is so low. Rather, the sulfate anions are excreted as ammonium sulfate. The concentration of titratable acidity usually does not vary much from day to day. Hence, if there is a need to substantially increase renal acid excretion, titratable acidity is not the answer.

In the presence of MA, the kidney increases urinary H^+ excretion in the form of ammonium (NH_4^+). Ammonia (NH_3) buffering occurs via the following reaction:

$$NH_3 + H^+ \leftrightarrow NH_4^+$$

Ammonium is produced in the PT and secreted into the proximal tubular lumen by replacing H^+ in the apical Na^+/H^+ antiporter. Ammonium is then reabsorbed in the loop of Henle, where it replaces K^+ in the apical Na^+-K^+-$2Cl^-$ cotransporter. In the medullary interstitium of the thick ascending limb, NH_4^+ dissociates back into NH_3 and H^+. The NH_3 diffuses into the lumen of the CD, where it is available to buffer H^+ ions and becomes NH_4^+. Ammonium is trapped in the lumen and excreted as the chloride salt. The kidney can adjust the amount of NH_3 synthesized to meet demand, making this a powerful system to buffer secreted H^+ in the urine. For every molecule of H^+ that is buffered by NH_3, a molecule of HCO_3^- is formed and released into the blood.

USE OF ANION GAP IN THE EVALUATION OF METABOLIC ACIDOSIS

The serum anion gap (AG) represents the difference between unmeasured anions and unmeasured cations. It is calculated as follows:

$$AG = (Na^+ + K^+) - (Cl^- + HCO_3^-) \text{ (normally 14-16 mmol/l)}$$

Since the change in serum potassium concentration is small, potassium is often omitted from the calculation. Therefore,

$$AG = Na^+ - (Cl^- + HCO_3^-) \text{ (normally 10-12 mmol/l)}$$

The major unmeasured anions in serum include albumin, phosphate, sulfate, and other organic anions. The major unmeasured cations in serum include calcium, magnesium, and other less-abundant cations. An increase in the AG may be due to a decrease in unmeasured cations or an increase in unmeasured anions. When unmeasured anions, such as acetoacetate in diabetic ketoacidosis or lactate in lactic acidosis, accumulate in the body, the AG increases because the H^+ will buffer the bicarbonate causing the fall in serum bicarbonate, while the retained anions (lactate or acetoacetate) will add to unmeasured anions. The loss of bicarbonate either from the gastrointestinal tract (e.g., diarrhea) or the kidney (e.g., RTA) will lead to hyperchloremic MA because the loss of bicarbonate must be accompanied by the rise of serum chloride to maintain electroneutrality. The level of serum albumin also influences the serum AG. For every fall of serum albumin of 1 g/dL, the AG drops by about 4 mmol/l. An increase of unmeasured cations as seen with the accumulation of cationic immunoglobulins in patients with plasma cell dyscrasia can also decrease the AG.

HIGH ANION GAP METABOLIC ACIDOSIS

There are four principal causes of a high AG MA (Table 1). Lactic acidosis is an acidosis caused by either lactic acid overproduction due to tissue hypoxia (e.g. shock) or underutilization (e.g., liver disease, thiamine deficiency). D-lactic acidosis is another unique form of lactic acidosis, which occurs in patients with short-bowel syndrome. The patients present with recurrent episodes of encephalopathy and MA.[5] D-lactate is not measured routinely when lactate levels are ordered and must be requested specifically when such cases are suspected. Ketoacidosis occurs when delivery of free fatty acids to the liver or preferential conversion of fatty acids to ketoacids (acetoacetate, β-hydroxybutyrate) is increased. This pathway is favored when insulin is absent, as in the fasting state (starvation ketoacidosis), in insulin-dependent diabetes mellitus (diabetic ketoacidosis), and when glucagons and cortisol action is enhanced (alcoholic ketoacidosis). Renal failure, both acute and chronic, can also cause high AG MA. It is largely due to a decrease in ammonium excretion as a result of reduced renal mass. Ingestion of toxins such as ethylene glycol, methanol and salicylate are well known causes of high AG MA. Less common causes include pyroglutamic acid (5-oxoproline), propylene glycol and djenkol bean (djenkolism). Pyroglutamic acidemia has been reported in patients after acetaminophen exposure.[6] Affected patients present with severe high AG MA accompanied by alterations in mental status ranging from confusion to coma. High concentrations of pyroglutamic acid are found in the blood and urine parallel to the increase in the AG. Propylene glycol, a solvent used in pharmaceutical preparations, has been reported to cause a high AG MA with an elevated osmolal gap, primarily in patients receiving lorazepam in doses exceeding the upper limit of the recommended dosage range (0.1 mg/kg per hr).[7] Ingestion of djenkol beans, which is commonly found in Indonesia and Malaysia, may cause acute renal failure and high AG MA.[8] The beans have a lot of djenkolic acid. The affliction status of individuals is different, so at a large gathering of people eating the same beans, some will develop acute renal failure while others won't. It is not clear how these beans induce acute renal failure. Mostly men are affected. The chief complaint is loin pain, suprapubic tenderness and hematuria. The urinalysis shows hematuria, granular casts and needle-shaped crystals.

Table 1. Causes of High Anion Gap Metabolic Acidosis

Lactic acidosis
Type A and B lactic acidosis
D-lactic acidosis
Ketoacidosis
Diabetic
Alcoholic
Starvation
Renal failure (acute and chronic)
Intoxication
Ethylene glycol
Methanol
Salicylate
Pyroglutamic acid (5-oxoproline)
Propylene glycol
Djenkol bean (djenkolism)

HYPERCHLOREMIC (NORMAL ANION GAP) METABOLIC ACIDOSIS

The differential diagnosis of hyperchloremic MA is outline in table 2. Diarrhea causes the loss of large quantities of bicarbonate and can results in a MA, especially when the kidney is unable to adapt to the loss by increasing net renal acid excretion. The intestinal mucosa has an apical Cl^-/HCO_3^- exchanger. When urine is diverted to a loop of bowel such as occurs in ureterosigmoidostomy, the chloride in the urine is exchanged for HCO_3^-, leading to hyperchloremic MA. The typical findings in proximal and distal RTA include hypokalemia with hyperchloremic MA because of renal bicarbonate loss (proximal RTA) or impaired net H^+ secretion (distal RTA). Chronic kidney disease can lead to MA when the glomerular filtration rate is between 30 to 59 mL/min (stage III). Several drugs such as ACE

Table 2. Causes of Hyperchloremic (Normal Anion Gap) Metabolic Acidosis

Gastrointestinal bicarbonate loss
Diarrhea
Urinary tract diversion to intestine (ureterosigmoidoscopy, ileal conduit)
Intestinal fistula
Drugs (laxative abuse, magnesium sulfate, cholestyramine)
Renal acidosis
Hypokalemia (proximal and distal RTA)
Hyperkalemia (type IV RTA, aldosterone deficiency, aldosterone resistance)
Normokalemia (early renal failure/stage III chronic kidney disease)
Drug-induced hyperkalemia (with renal insuffi ciency)
ACE inhibitors
Potassium sparring diuretics (spironolactone, amiloride, triamterene)
Trimethoprim
Pentamidine
NSAIDS
Cyclosporine
Administration of chloride containing fluid (ammonium chloride, hyperalimentation, rapid saline administration)
Others (hippurate, cation exchange resins)

inhibitors, spironolactone, amiloride, trimethoprim, pentamidine, nonsteroid anti inflammatory drugs (NSAIDs) and cyclosporine can induce hyperkalemia with hyperchloremic MA. The administration of an acid that contains Cl^- as an ion (e.g., NH_4Cl) can result in a hyperchloremic MA. Infusion of arginine or lysine hydrochloride during parenteral hyperalimentation can have the same result. If isotonic saline is infused rapidly, the serum bicarbonate will decline reciprocally in relation to an increase in serum chloride, leading to hyperchloremic MA.

CONTROVERSIES IN THE TREATMENT OF ACUTE METABOLIC ACIDOSIS

Treatment of acute MA, in particular organic forms of acidosis such as lactic acidosis and ketoacidosis, has remained very controversial for a long time in clinical medicine.[9,10] Although most clinicians would agree that elimination of the causes of the acidosis such as treatment of shock, restoration of the circulating fluid volume, improvement or augmentation of cardiac function and amelioration of sepsis, is essential, there is disagreement as to whether improvement of the acidosis by administration of base is beneficial. The severity of the MA, as determined by blood pH, has been a predictor of mortality, i.e., the more severe the acidosis the greater the mortality.[11] Whether this is a causal relationship or whether the severity of the MA is a reflection of the severity of the underlying disease, has not been elucidated.

The detrimental consequences of severe acidemia are numerous (Table 3). Acute MA has been shown to have multiple effects on organ and cellular function, including decreased cardiac output, predisposition to arrhythmias, hypotension due to vasodilatation of resistance vessels, increase in pulmonary vascular resistance, reduced action of catecholamines, impaired oxygen delivery, decreased energy generation and impaired glucose metabolism. The combined effects of these perturbations can potentially lead to increased patient morbidity and possibly mortality.

Table 3. Adverse Consequences of Severe Acidemia

Cardiovascular
Decreased cardiac output
Predisposition to cardiac arrhythmias
Hypotension due to a decrease in peripheral vascular resistance
Centralization of blood volume with increase in pulmonary vascular resistance
Resistance to cathecholamines
Central nervous system
Decreased sensorium
Gastrointestinal
Gastric atony
Reduced hepatic blood flow
Metabolic
Increased binding of oxygen to hemoglobin with reduced oxygen delivery
Reduction in ATP synthesis
Insulin resistance
Increase in ionized calcium levels

Given the potential deleterious consequences of severe acidemia, it is reasonable to administer alkali with the hope of reversing or ameliorating many of the negative effects of acidosis, especially those affecting the cardiovascular system. Sodium bicarbonate remains the mainstay of alkali therapy. Other alkalinizing salts, such as sodium lactate, citrate, or acetate, are not reliable substitutes, since their alkalinizing effect depends on oxidation to bicarbonate, a process that can be seriously impaired in several clinical conditions (e.g., liver disease). Experimental study has shown that administration of bicarbonate failed to improve hemodynamic effect or reduce the mortality of animals with lactic acidosis.[12] Controlled clinical studies in humans with lactic acidosis also revealed no hemodynamic benefit of sodium bicarbonate administration.[13,14]

REASONS FOR FAILURE OF SODIUM BICARBONATE THERAPY IN ACUTE ORGANIC METABOLIC ACIDOSIS

The failure of sodium bicarbonate administration to reduce the morbidity and mortality of acute organic MA despite improvement in acid-base parameters is counterintuitive. Potential reasons include: (1) despite the increase in extracellular pH, an exacerbation of intracellular acidosis occurs with bicarbonate administration due to the initial rapid influx of CO_2 with resultant impairment of organ function; (2) calcium and H^+ compete with each other to bind albumin and as blood pH is elevated with sodium bicarbonate administration, more calcium will bind to albumin leading to a reduction of ionized calcium that depresses cardiac output; (3) removal of a protective effect provided by acidosis against hypoxic damage; and (4) acceleration of cellular influx of sodium and calcium in response to worsening intracellular acidosis by bicarbonate administration, which can induce cellular swelling and dysfunction.

ALTERNATIVE THERAPY FOR ACUTE METABOLIC ACIDOSIS

Concern about the potential deleterious effect of sodium bicarbonate therapy led to the development of other forms of base or modes of base delivery that could be used to improve acid-base balance. Carbicarb which consists of equimolar concentrations of sodium bicarbonate and sodium carbonate has been used as a buffer similarly to sodium bicarbonate but without the net generation of CO_2.[15] However, the results from clinical trials are sparse without any controlled human trials. THAM (tris-hydroxymethylamino-methane) is sodium-free compound that has a free amino group to buffer protons. Like Carbicarb, THAM limits CO_2 generation and unlike sodium bicarbonate, THAM increases both extracellular and intracellular pH. THAM has been used by clinicians for the treatment of acid-base disorders for a long time.[16] Although theoretically THAM is a valuable buffer, it has not been widely used because it is eliminated primarily by the renal route and might not be very useful in the presence of significant renal impairment. Moreover, serious side effects, including hyperkalemia, hypoglycemia, respiratory depression, venous sclerosis in cases of extravasation, and hepatic necrosis in neonates, has been reported and markedly limit its usefullness.[16] Dichloroacetate is another compound that has been used in acute MA. However, in a randomized controlled trial in patients with lactic acidosis, dichloroacetate failed to improve hemodynamics or outcome.[17] Hemofiltration and continuous renal replacement therapies have been advocated as treatments for lactic acidosis. However, kinetic studies of lactate removal do not suggest that removal can counteract lactate production in any meaningful way.

RISK OF SODIUM BICARBONATE THERAPY

The potential risk of sodium bicarbonate administration are volume overload, hyperosmolality, hypernatremia, overshoot metabolic alkalosis and a rise in $PaCO_2$, which can become problematic in patients with reduced ventilatory reserved. Infusion of large amount of undiluted 1 N or 8.4% $NaHCO_3$ (containing 1000 mmol of sodium per liter) can give rise to hypernatremia and hyperosmolality. This complication can be avoided by adding 75-ml of 8.4% $NaHCO_3$ to each 500-ml of 5 percent dextrose in water, thereby rendering these solutions nearly isotonic. Since adverse effects of MA appear to be more severe when blood pH falls below approximately 7.2, this level of blood pH has often been chosen by many clinicians as the point at which to begin therapy. Also, many clinicians target a blood pH of 7.2 or greater as their goal for base therapy. However, controlled studies to determine the optimal target blood pH and how rapidly it should be achieved have not been done.

How much bicarbonate need be given? There is no simple prescription since many confounding factors can affect the acid-base status. As a rule of thumb, assuming the space of distribution of bicarbonate is 50% of body weight, bicarbonate deficit can be calculated by using the following equation:

$$HCO_3^-\ \text{deficit} = (\text{desired serum } HCO_3^- - \text{measured } HCO_3^-) \times 0.5 \times \text{body weight}$$

To prevent overtreatment, serum bicarbonate should not be raised above 12 mmol/l in the initial correction. Thus to raise serum bicarbonate from 4 mmol/l to 10 mmol/l in a 60-kg patient, one should administered 6 x 0.5 x 60, or 180 mmol of sodium bicarbonate, which should be given by adding 75-ml of 8.4% $NaHCO_3$ to each 500-ml of 5 percent dextrose in water (containing 75 mmol of sodium and bicarbonate). This amount of bicarbonate should be infused over a period of several hours rather than as a bolus. Some text books still recommend full correction of serum bicarbonate to normal levels.[18] Thus to raise serum bicarbonate from 4 mmol/l to normal levels of 24 mmol/l in a 60-kg patient; one should administered 20 x 0.5 x 60, or 600 mmol of sodium bicarbonate. The administration of this a mounts of sodium bicarbonate is potentially dangerous because it can induce severe hypernatremia and overshoot alkalosis.

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