Metabolic Acidosis in Patients with Gastrointestinal Disorders: Metabolic and Clinical Consequences

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Patients with ileostomies, biliary or pancreatic drainage may develop significant metabolic acidosis due to enteric bicarbonate loss and volume depletion. Acutely, the metabolic acidosis is likely well tolerated, but over time can lead to protein catabolism, bone and mineral abnormalities and hormonal alterations that can impair health. Bicarbonate supplementation has been studied in other situations of chronic metabolic acidosis and has shown some benefit in improving metabolic status. Patients with metabolic acidosis due to gastrointestinal disorders should also receive consideration for bicarbonate supplementation. The various methods for achieving this goal are discussed.

INTRODUCTION

Maintenance of a constant hydrogen ion concentration (pH) is critical for health. Among the reasons a constant pH is important is that enzymatic reactions have a "pH optimum" that is crucial for allowing maximal enzyme activity (1). Consequently, changes in pH will affect enzyme activity and thereby disrupt critical metabolic pathways. Secondly, the tertiary structure of protein changes when pH rises or falls (1). A structural change in a protein can disrupt its function and also accelerate the degradation of the protein through cellular processes (2). Two organs, the

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kidneys and lungs, along with intra- and extracellular buffer systems, work together to prevent changes in the blood or tissue pH.

Clinical studies in many patient populations (infants, children, adults, patients with chronic kidney disease (CKD)) document adverse effects of metabolic acidosis (3). These may include: protein malnutrition, bone loss and hormonal abnormalities (3). In patients with gastrointestinal (GI) disease, loss of substantial amounts of bicarbonate (usually associated with diarrheal states) can lead to a serious metabolic acidosis (4). In those patients with long-standing and continuous GI bicarbonate losses, the development of a chronic metabolic acidosis is likely to have deleterious effects similar to other chronic acidotic states and aggressive treatment with bicarbonate supplementa-

Table 1
Acid-base Abnormalities Associated with Gastrointestinal Disorders

Gastrointestinal disorder	Acid-base abnormality
Vomiting, nasogastric suction	Metabolic alkalosis
Diarrhea States	
– Cholera	Metabolic acidosis
– Other infectious	Metabolic acidosis
– Congenital chloridorrhea	Metabolic alkalosis
Pancreatic/biliary drainage	Metabolic acidosis
Jejunostomy or ileostomy drainage	Metabolic acidosis or alkalosis
Short bowel	Metabolic acidosis

tion is likely warranted. This review will focus on those GI disorders that lead to metabolic acidosis, the potential consequences of long-standing metabolic acidosis and therapy of these conditions.

METABOLIC ACIDOSIS IN GASTROINTESTINAL DISORDERS

The GI tract can be thought of as a key player in total body acid-base balance. In a typical day, large amounts of H^+ and HCO_3^- traverse the specialized epithelia of the various gut segments (5). However, under normal circumstances, only a small amount of alkali (approximately 30 to 40 mmol) is lost in the stool per day (5). This small amount of alkali lost in the stool is easily regenerated by net renal acid excretion, which is tightly regulated to maintain total body alkali stores and acid-base balance. Disruption of normal gut function, however, can uncover the potential of gut transport processes to overwhelm acid-base homeostasis. Depending upon the site of the GI tract that is affected (Table 1), either metabolic acidosis or metabolic alkalosis can occur depending upon the specific nature of the fluid loss.

Diarrhea

For acid-base and electrolyte abnormalities to occur in diarrheal states, the volume of enteric fluid that is lost

must be large in order to overwhelm the ability of the kidney to maintain acid-base balance. The predominant acid-base abnormality that develops is determined by the specific electrolyte content of the fluid that is lost (6,7). As shown in Table 2, various disease states lead to varying amounts of sodium, chloride and bicarbonate loss and these losses vary widely. Those conditions that are associated with more chronic states of metabolic acidosis are laxative abuse, biliary and pancreatic drainage, and ileostomy drainage (7).

Laxative Abuse

The major clinical electrolyte disorder associated with laxative abuse is hypokalemia (8). Acid-base abnormalities tend to be mild and can range from mild metabolic alkalosis to metabolic acidosis depending upon the volume of stool bicarbonate losses (9). Hypokalemia in this setting may offer some mild protection from the development of metabolic acidosis due to (1) movement of H^+ into cells (as potassium leaves cells to buffer the stool potassium losses), raising the extracellular bicarbonate concentration and (2) an increase in renal ammonium production and excretion allowing an increase in renal H^+ excretion. However, if stool losses are large, metabolic acidosis can ensue secondary to the large enteric bicarbonate losses.

Biliary and Pancreatic Drainage

This fluid is extremely rich in bicarbonate; however, the volume associated with drainage of this fluid is relatively low, limiting the degree of ensuing metabolic acidosis. However, in the setting of biliary or pancreatic fistulas or external drains, there may be massive loss of bicarbonate rich fluids leading to both metabolic acidosis, as well as volume depletion which helps to maintain the acid-base abnormality (6,7).

Ileostomy Drainage

Typical daily output in patients with well-functioning ileostomies with intact ileum are 200 to 1000 mL of fluid, 40 to 100 mmol of sodium, 15 to 30 mmol of bicarbonate and 5 mmol of potassium (7,10–12). With these typical losses, most patients are able to maintain fluid, electrolyte and acid-base balance. However, this

Table 2
Volume and Electrolyte Composition in Diarrheal Fluid and Ileostomy Drainage

Disease state	Volume (L/day)	Sodium mmol/L	Potassium mmol/L	Chloride mmol/L	HCO_3^- mmol/L
Normal stool	<0.15	20–30	55–75	15–25	0
Diarrhea					
– Inflammatory	1–3	50–100	15–20	50–100	10
– Secretory	1–20	40–140	15–40	25–1-5	20–75
– Chloridorrhea	1–5	30–80	15–60	120–150	<5
– Villous adenoma	1–3	70–150	15–80	50–150	no data
Ileostomy or jejunostomy drainage					
– New	1–1.5	115–140	5–15	95–125	30
– Adapted	0.5–1.0	40–90	5	20	15–30

is a tenuous balance and patients may easily develop significant volume depletion, electrolyte and acid-base disturbances (metabolic acidosis) if ileostomy output increases or if dietary intake is disrupted or altered (13). The metabolic acidosis is generally maintained by significant extracellular volume depletion and an acute decline in glomerular filtration rate (14,15).

EFFECTS OF CHRONIC METABOLIC ACIDOSIS (TABLE 3)

Patients suffering from chronic metabolic acidosis are subject to numerous detrimental effects that include protein malnutrition and catabolism, bone and mineral disorders and alterations in endocrine function.

Protein Malnutrition and Catabolism

Experimental studies, largely in patients with advanced renal disease and in animal models, have demonstrated that metabolic acidosis leads to loss of muscle mass through several different, but inter-related pathways (16,17). It is important to state that there are no long-term studies in patients with long-standing metabolic acidosis due to GI sources and thus all of the following data must be extrapolated to this particular circumstance. In almost all studies, induction of acidosis has led to amino acid and protein catabolism, negative nitrogen balance, suppressed albumin synthesis and

Table 3
Consequences of Metabolic Acidosis

1. Nutritional
   a. Catabolic effects
   b. Anti-anabolic effects
   c. Insulin resistance

2. Bone Disease
   a. Physiochemical dissolution of bone
   b. Decreased osteoblast function
   c. Increased osteoclast function
   d. Increased level and effect of parathyroid hormone
   e. Possible decreased activity of 1-α hydroxylase and production of active vitamin D

3. Hormonal effects (Table 4)

increased proteolysis (16,17). The first of these mechanisms involves the catabolism of amino acids due to the need to stimulate renal ammonia production in order to increase acid excretion (18,19). The second mechanism involves total protein catabolism. In chronically uremic rats, restoration of normal serum pH reduces protein catabolism to normal levels and it is clear that metabolic acidosis overrides the body's normal adaptive

Table 4
Hormonal Responses to Chronic Metabolic Acidosis

Hormone	Effect of Acidosis
Growth hormone (GH)	• Decreased GH secretion • Decreased IGF-1 response
Insulin	• Suppressed insulin-mediated glucose metabolism
Insulin-like growth factor-1 (IGF-1)	• Decreased levels in plasma, kidney, liver
Thyroid hormone	• Decreased plasma T3 and T4 levels • Increased plasma TSH
Glucocorticoids	• Increased production of glucocorticoids
Parathyroid hormone	• Decreased sensitivity of PTH secretion to changes in plasma calcium

responses to a low-protein diet (suppression of the oxidation of essential amino acids and the degradation of protein) (18,19). Similar to these animal studies, Papadoyannakis, et al found that correction of metabolic acidosis led to improvement in nitrogen balance in six CKD patients (20).

Alterations in Hormonal Systems (Table 4)

Endocrine alterations are critically important in contributing to the catabolic and anti-anabolic effects of metabolic acidosis. Acidosis stimulates an increase in glucocorticoid levels which are critically important in supporting the catabolic state seen in acidosis (16, 17). Acidosis also interferes with the effects of insulin and insulin-like growth factor-1 (IGF-1) on cellular signaling and may induce insulin resistance in peripheral tissues (21). Acidosis also may reduce the release of growth hormone (2).

The available evidence suggests that metabolic acidosis is associated with an increase in PTH levels, at least in patients on chronic dialysis and may exacerbate secondary hyperparathyroidism (22). Finally, acidosis lowers serum levels of free T3 and T4, which may also impair anabolic pathways (23).

Effects on Bone and Mineral Metabolism

One of the costs of trying to maintain a stable serum bicarbonate level in the face of an uncorrected metabolic acidosis is the dissolution of bone buffers and net efflux of calcium from bone (24,25). Acid loading in normal individuals is associated with hypercalciuria and hyperphosphaturia, suggesting that bone is a major site for the extracellular buffering of the retained acid (26). Supporting this idea, metabolic acidosis is associated with decreases in the content of bone bicarbonate (27). Interestingly, bicarbonate supplementation of patients with metabolic acidosis due to renal tubular abnormalities with normal renal function is associated with decreases in urinary calcium, phosphorus and hydroxyproline supporting the concept of significant effects of even mild acidosis on bone health (28).

INTERVENTIONAL STUDIES TO IMPROVE ACIDOSIS AND RECOMMENDED LEVEL OF SERUM BICARBONATE

The majority of studies that have addressed the clinical implications of bicarbonate supplementation to improve acidosis have been done in patients with CKD and are limited due to small size (16,17). For example, Seyffart, et al showed a significant increase in body weight in 11 of 21 patients with therapy to improve metabolic acidosis (29). Two other studies have documented improved serum albumin levels with normalization of acid-base status (30,31). In 2006, the Cochrane Collaboration reviewed the issue of whether correction of chronic metabolic acidosis for patients with CKD on dialysis was supported by evidence. The final conclusion of the Cochrane report was "there

may be some beneficial effects on both protein and bone metabolism, but the trials were underpowered to provide robust evidence (32)."

In 2000, the National Kidney Foundation (NKF) Kidney Disease Outcomes Quality Initiative reviewed the data on the implications of chronic metabolic acidosis and stated that the optimum serum bicarbonate and blood pH needed to be defined (33). However, based upon the limited data available, they recommended that serum bicarbonate levels should be maintained at or above 22 mmol/L. Extrapolating this data to other patient populations is problematic. However, given the known deleterious effects of acidosis on numerous metabolic pathways, the recommendation from the NKF is a reasonable one to use in other patients with conditions associated with chronic metabolic acidosis. Alternatively, it is possible, although labor-intensive and costly, to measure nitrogen balance, perform careful nutritional assessments and measure markers of bone metabolism in patients with chronic metabolic acidosis to gain an understanding of the effects in any given patient. In those patients, who are clearly suffering metabolic derangements, a trial of bicarbonate supplementation would be indicated.

SUPPLEMENTATION OF BICARBONATE

The amount of bicarbonate (and form of replacement) will vary considerably depending on: 1) the degree of acidosis, 2) ongoing metabolic acid production, 3) ongoing GI losses, 4) the rapidity to which the acidosis needs to be corrected, 5) renal function and the ability of the kidney to regenerate new bicarbonate and, 6) the ability of the patient to take and tolerate oral vs. intravenous supplementation. Obviously, a patient with large ongoing enteric bicarbonate losses will need continued bicarbonate supplementation vs. a patient with transient loss of enteric bicarbonate that may need a few doses to replete bicarbonate losses. Furthermore, patients with significant CKD may need larger doses of bicarbonate to support the inability of the diseased kidney to regenerate new bicarbonate. On a normal Western diet, patients generate approximately 1 mEq/kg body weight/day of acid that needs to be buffered (34). However, this value may vary considerably if protein intake is high (higher acid generation)

or low (low acid generation) or if the patient is markedly catabolic (high acid generation).

In order to estimate the amount of bicarbonate supplementation that may be required, the bicarbonate deficit can be calculated from the following formula:

$$\text{Bicarbonate deficit} = (0.6 \times \text{body weight}) \times (\text{desired bicarbonate} - \text{actual bicarbonate})$$

This amount of bicarbonate can be given over several hours intravenously to correct the deficit, but it is important to remember that this is only an approximation and serial laboratory measurements are required. Furthermore, continued bicarbonate supplementation will be required to replace ongoing losses from the GI tract or the inability of the kidney to regenerate bicarbonate if applicable.

An arterial blood gas is not needed prior to therapy as the key point is that the pH may be maintained within relatively normal limits due to compensatory changes and the metabolic complications of acidosis are dependent on the serum bicarbonate and not necessarily the pH.

It is also important to recognize that the degree to which exogenous bicarbonate will raise the plasma bicarbonate concentration is dependent upon the time at which the plasma level is drawn in comparison to when the dose is given (and not stop supplementation prematurely as a result). Initially, the added bicarbonate is limited to the vascular space and a large increase in plasma bicarbonate level is typically seen. However, over time, the exogenous bicarbonate equilibrates through the total extracellular fluid and then through the intracellular and bone compartments lowering the plasma bicarbonate level. Thus, a plasma level of bicarbonate measured 20 minutes after bicarbonate replacement will lead to a large rise in plasma bicarbonate, but when the plasma bicarbonate is measured several hours later, the rise will be much lower (1).

Finally, in replacing bicarbonate it is important to monitor for concomitant changes in plasma potassium. Potassium depletion is common in patients with metabolic acidosis associated with GI losses. However, the initial potassium level may be normal since the metabolic acidemia causes extracellular shift of potassium. Thus, when the acidemia resolves with bicarbonate supplementation, it is common for the potassium

Table 5
Bicarbonate and Equivalent Replacement Suggestions

Bicarbonate Source	Dose for 1 mEq bicarbonate	Dose for 20 mEq bicarbonate
Na Bicarbonate tablets	• Approximately 100 mg • Each 650 mg tablet contains 7.74 mEq of bicarbonate	Approximately 3 × 650 mg tablets
Citrate, bicitra®, cytra-2®, Shohl's solution, oracit®, polycitra-K®	• All contain 1–2 mEq/mL of bicarbonate equivalent (citrate is converted to bicarbonate)	Approximately 20 mL NOTE: it is important to note if the solution contains potassium or not to avoid inadvertent potassium excretion
Acetate (added to TPN or IV fluids)	• Each mEq of acetate generates 1 mEq of bicarbonate—the dose depends on the specific dilution in the fluid given	
Bicarbonate (added to IV fluids)	• The dose depends on the specific dilution in the fluid given	

Example: 70 kg pt w/ serum bicarbonate level chronically ~15 mEq/L:

   Bicarbonate deficit (to replace to normal bicarbonate of 24 mEq/L): 378 mEq

If this deficit was to be replaced:

   Intravenously: IV 5% dextrose in water with 150 mEq/L sodium bicarbonate:

   Each liter would replace 150 mEq of bicarbonate: 2.52 Liters—typically replaced at 75–100mL/hr, then, daily replacement in preparation for home would need to be initiated depending upon amount of ongoing losses

   Oral w/ sodium bicarbonate tablets: would require a total of 49 tablets divided into multiple doses—typically as 2 tablets three times daily

   Orally/enterally w/ Shohl's solution: would require 378 mL of solution divided into multiple doses—typically replaced in 30 mL doses given 2 to 4 times daily

NOTE: calculations of the amount of bicarbonate replacement are estimates and serial laboratory testing MUST occur to ensure that the replacement is adequate and that no other electrolyte abnormalities are occurring

deficit to be revealed and many patients will require significant potassium supplementation.

Methods of Bicarbonate Supplementation

There are several methods of delivering bicarbonate to patients with metabolic acidosis. These forms differ in being given either orally or intravenously and whether the base is bicarbonate or another anion that can be converted by the liver to bicarbonate (such as citrate or acetate) (Table 5).

Sodium bicarbonate is available either in tablet form or may be given intravenously. Tablets are available in sizes from 325 mg to 650 mg and each 1 gram of sodium bicarbonate equals 11.9 mEq of sodium and bicarbonate. The usual adult daily dose can range from 325 mg to 2 grams orally four times per day depending upon the individual need. Precautions should be taken in patients with congestive heart failure given the excess sodium load and possibility of precipitating

volume overload. Sodium bicarbonate may also cause stomach cramps, flatulence and vomiting and there have been case reports of stomach rupture (35,36). Due to the effects on systemic pH, stomach acidity and urine pH, the metabolism of numerous drugs can be affected and the packet insert for medications should be consulted to ensure that drug disposition is not affected. The intravenous form of sodium bicarbonate is available as a hypertonic solution (8.4%) that must be diluted to isotonicity (1.5%) before intravenous infusion. The 8.4% solution of sodium bicarbonate equals 1 mEq/mL of bicarbonate. Care must be exercised with intravenous bicarbonate infusion to avoid volume overload, an overshoot metabolic alkalosis, hypernatremia, or hypercapnia. Furthermore, many total parenteral nutrition solutions and other IV medications are incompatible with bicarbonate addition, however, acetate is an available alternative that is routinely added to TPN.

Citric acid is available in numerous forms (sodium citrate, potassium citrate, citric acid) either in tablets or as syrups/solutions. The syrups/solutions contain potassium and/or sodium citrate and citric acid and provide citrate sufficient to generate 1–2 mEq of bicarbonate per mL. Numerous proprietary solutions exist and differ in whether they contain potassium citrate (for example, polycitra-K®) or not (for example, bicitra®, cytra-2®, Shohl's solution, oracit®). Caution should be exercised in prescribing these agents to ensure that the patient is not receiving inadvertent potassium supplementation. The solutions offer the advantage of allowing significant amounts of bicarbonate supplementation in a more convenient form. For example, 30 mL of Shohl's solution given three times daily provides 90 mEq of bicarbonate supplementation that would otherwise require 7.5 grams of sodium bicarbonate tablets (or 10–14 tablets per day). Of note, Shohl's solution often contains sorbitol, hence may aggravate diarrhea in some patients.

Potassium citrate is available in 10 mEq tablets and provides an equivalent of 10 mEq of bicarbonate per tablet and can be utilized to supplement both potassium and bicarbonate losses.

Since citrate requires hepatic conversion to bicarbonate, patients with severe hepatic impairment may develop hypocalcemia and a worsening metabolic aci-

dosis due to the inability to convert citrate to bicarbonate. However, this is extremely uncommon and most patients with hepatic impairment do not have difficulties with this metabolic conversion. Other side effects of citric acid based therapy include: diarrhea, nausea, and vomiting (especially at higher dosages).

For patients receiving total parenteral nutrition (TPN), bicarbonate is best supplied as sodium acetate, which can be converted in the liver to bicarbonate. Acetate is much more stable than bicarbonate in TPN and can be converted to bicarbonate on an equimolar basis even in patients with severe liver dysfunction.

OTHER THERAPIES FOR GI-DISEASE ASSOCIATED METABOLIC ACIDOSIS

Most patients with GI-disease related metabolic acidosis will have concomitant volume depletion (7). Patients with ileostomies are particularly prone to volume depletion which can prevent correction of the metabolic acidosis. Thus, some patients may require IV volume replacement.

Maneuvers to decrease ostomy output are critically important in the management of these patients. A study by Kramer, et al investigated the optimal daily sodium intake for patients with ileostomies and demonstrated that sodium intake of 2.5 to 3.5 grams/day is required to maintain sodium balance and does not significantly increase ileal drainage output (37). Foods that increase ileal output should also be avoided (13). Drugs can also be utilized to decrease ostomy output. Codeine phosphate will decrease the ileal excreta volume as well as sodium, potassium and water losses (38,39).

CONCLUSIONS

Patients with chronic GI conditions such as high-output ileostomies or pancreato-biliary fistulas are at risk for the development of chronic metabolic acidosis. Based upon data mostly from patients with advanced chronic kidney disease, it is clear that chronic metabolic acidosis has detrimental effects on protein stores, bone and mineral metabolism and hormonal systems. In several studies, repletion of bicarbonate losses has led to improved nutritional parameters. Thus, it seems rea-

sonable to attempt correction of bicarbonate levels to at least 22 mEq/dL in patients with chronic metabolic acidosis (as recommended for patients with chronic kidney disease). However, controlled studies are required in patients without chronic kidney disease to support this recommendation. Certainly, those patients with chronic metabolic acidosis should be closely monitored for changes in protein balance, evidence for malnutrition and changes in bone and mineral metabolism. If these patients demonstrate nutritional consequences of metabolic acidosis, a more aggressive strategy of bicarbonate supplementation is warranted. ■

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