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Treatment of Metabolic Acidosis in Patients With CKD

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Abstract

Metabolic acidosis is a common complication of chronic kidney disease and believed to contribute to a number of sequelae, including bone disease, altered protein metabolism, skeletal muscle wasting, and progressive GFR loss. Small trials in animal models and humans suggest a role for alkali therapy to lessen these complications. Recent studies support this notion, although more definitive evidence is needed on the long-term benefits of alkali therapy and the optimal serum bicarbonate level. The role of dietary modification should also be given greater consideration. In addition, potential adverse effects of alkali treatment must be taken into consideration, including sodium retention and the theoretical concern of promoting vascular calcification. This teaching case summarizes the rationale for and the benefits and complications of base therapy in patients with chronic kidney disease.

Index Words

metabolic acidosis; chronic kidney disease; bicarbonate; alkali therapy

INTRODUCTION

Metabolic acidosis is associated with many of the complications of chronic kidney disease (CKD), including bone disease, muscle protein catabolism, and progressive glomerular filtration rate (GFR) loss. The Kidney Dialysis Outcomes Quality Initiative (KDOQI) guidelines, based on “evidence and opinion,” call for maintenance of serum bicarbonate ≥22 mEq/L to lessen these complications.[1] A 2007 Cochrane review of alkali therapy in CKD found insufficient evidence for benefit.[2] The evidence base has expanded since then and lends further support to the benefits of alkali therapy. However, a definitive randomized clinical trial has not yet been performed.

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CASE REPORT

Clinical History and Initial Laboratory Data

A 58-year-old man with a history of sickle cell disease, hepatitis B, hypertension, and CKD stage 4 was seen in renal clinic. He had a progressive decline in kidney function over 13 years with a urine protein-to-creatinine ratio of 1.7 g/g. His kidney function had been stable for the past 2 years. Medications included nifedipine 60 mg daily, calcitriol 0.5mg daily, and folic acid. Physical examination revealed a blood pressure of 130/72 mmHg and no peripheral edema or signs of heart failure. Relevant laboratory data from one month prior and the day of the visit appear in Table 1.

Additional Investigations

Prior laboratory showed a metabolic acidosis 7 years earlier with a serum bicarbonate of 20 mEq/L and an estimated GFR of 38 ml/min/1.73 m^2. Earlier urinalyses revealed a urine pH consistently above 6.0.

Diagnosis

Chronic metabolic acidosis (presumed given the lack of confirmatory pH and pCO_2) and hyperkalemia in the setting of CKD, sickle cell disease, and distal nephron dysfunction.

Clinical Follow-up

The patient was started on oral sodium bicarbonate 1300 mg three times daily and returned to the clinic one month later. The blood pressure was 156/82 mmHg with trace peripheral edema. Nifedipine was increased to 90 mg daily. Three months later, the blood pressure was 122/67 mmHg with no peripheral edema. A basic metabolic panel revealed improvement in the serum bicarbonate (Table 1). Calcitriol was increased to 1 mg daily due to the persistently elevated parathyroid hormone (PTH) level. A year later the patient was found to have decreasing kidney function thought to be secondary to progression of CKD and hypercalcemia. After cessation of calcitriol and normalization of the serum calcium, kidney function improved. Sixteen months later, serum bicarbonate was maintained between 23 and 25 mEq/L and the serum potassium remained in the normal range. There was a slight increase in serum albumin, but no change in body weight (77 to 79 kg).

DISCUSSION

Metabolic acidosis is a common complication of advanced CKD, present in 30-50% of individuals with eGFR <30 ml/min/1.73 m^2.[3-5] It develops mainly secondary to reduced kidney mass and an inability to excrete the daily acid load via ammoniagenesis. Patients with CKD and acidosis have a positive acid balance of approximately 10-20 mEq/day.[6-8] In a minority of patients, there is bicarbonate loss in the urine due to failure of renal bicarbonate conservation.[9] The degree of acidosis in CKD is usually not severe. In uncomplicated acidosis, the serum bicarbonate is typically greater than 12 mEq/L, the blood pH >7.2, and the anion gap variable.[9-11] The acidosis remains relatively stable, but can worsen as GFR declines.[3,6] Some patients with CKD maintain close to normal serum bicarbonate levels even with severely compromised kidney function, including patients with diabetes who often develop less severe acidosis.[12] Conversely, in patients with hypoaldosteronism or tubulointerstitial disease, metabolic acidosis often occurs with eGFR >30 ml/min/1.73 m^2.[13,14] The patient in this case developed metabolic acidosis before the eGFR fell below 30 ml/min/1.73 m^2 with a persistently high urine pH. This suggests collecting duct damage with impaired acidification related to the patient's sickle cell disease.

Low serum bicarbonate has been associated with increased mortality in patients with moderate and advanced CKD, as well as among patients receiving both peritoneal dialysis (PD) and hemodialysis.[15-18] Chronic metabolic acidosis may have various adverse effects in patients with CKD (Table 2) on bone disease, insulin resistance, and muscle wasting, and it may contribute to the progression of kidney disease. Chronic acidosis results in negative calcium balance from bone buffering, which is ameliorated by treatment with alkali.[19] There is so far no direct evidence that alkali therapy improves bone density in patients with pre-dialysis CKD. However, in children with renal tubular acidosis, sustained alkali therapy attained and maintained normal stature.[20] In postmenopausal women with normal kidney function, administration of potassium bicarbonate to neutralize endogenous acid improved calcium and phosphorus balance, reduced bone resorption, and increased bone formation.[21] Furthermore, in patients receiving hemodialysis, oral sodium bicarbonate supplementation to achieve pre-dialysis serum bicarbonate levels of 24 mEq/L decreased progression of secondary hyperparathyroidism in patients with high bone turnover and stimulated bone turnover in patients with low bone formation.[22] Treatment of acidosis may also increase the sensitivity of the parathyroid glands to calcium.[23] In our patient, PTH declined in the year after alkali therapy was initiated, but this may have been due to the concurrent increase in calcitriol dose.

A large body of evidence suggests that metabolic acidosis is an important contributor to muscle wasting in patients with CKD. Acidosis impairs insulin and insulin-like growth factor (IGF)-1 signaling, leading to skeletal muscle protein breakdown via activation of caspase-3 and the ubiquitin-proteasome system.[24,25] Chronic acidosis causes negative nitrogen balance and decreases albumin synthesis.[26] Treating acidosis ameliorates the insulin signaling defect and decreases muscle breakdown.[27,28] In a randomized, double-blind, placebo-controlled trial in 60 PD patients, oral sodium bicarbonate improved nutritional status and reduced hospitalizations.[29] Correction of acidosis in another single-blinded trial of 200 PD patients resulted in increased lean body mass and fewer hospitalizations. [30] Interventional studies in hemodialysis patients have been inconsistent, and limited by small sample sizes, lack of control groups, and unmasked interventions. In patients with CKD stage 4, oral sodium bicarbonate increased albumin levels and mid-arm muscle circumference after 12 months.[31] Currently, few studies have examined functional outcomes related to acidosis.[32,33] In one single-blinded pilot study, increased lower-extremity muscle strength was seen after 6 weeks of oral sodium bicarbonate.[34]

Metabolic acidosis may also contribute to the progression of CKD by promoting tubulointerstitial injury via ammonia-induced complement activation and endothelin and aldosterone activation.[35,36] In an open-label, randomized, prospective parallel-group study, de Brito-Ashurst et al. assigned 134 patients with CKD stage 4 and serum bicarbonate 16-20 mEq/L to oral sodium bicarbonate to maintain a bicarbonate level ≥23 mEq/L or to standard-of-care. Bicarbonate supplementation slowed the rate of GFR loss and reduced progression to end stage renal disease (ESRD) requiring dialysis.[31] Phisitkul et al. noted similar findings in patients with hypertensive nephropathy with serum total carbon dioxide <22 mEq/L.[37] Thirty patients prescribed sodium citrate were compared to 29 controls who were unable or unwilling to take the medication. After 24 months, urine endothelin-1 excretion was significantly lower in the treatment group, as was the rate of eGFR decline. Lastly, a 5-year randomized, placebo-controlled, blinded study compared sodium bicarbonate with placebo or equimolar sodium chloride (n=40 per group).[38] The rate of eGFR decline was slower in patients treated with sodium bicarbonate (-1.47±0.19 ml/min per year) than in those given placebo (-2.13±0.19 ml/min per year) or sodium chloride (-2.05±0.19 ml/min per year).

The decision to initiate treatment of metabolic acidosis should be based on the severity of the acidosis as well as consideration of the patient's clinical condition (Figure 1). Even large doses of alkali appear to be well-tolerated in individuals without edema who have preserved urine output. Given the variability of serum bicarbonate measurements, the presence of acidosis should be verified with a second measurement. In addition, in most cases the serum bicarbonate alone should not be the basis for starting treatment. A blood gas should be obtained to verify the acid-base disturbance, especially if there is suspicion of a respiratory disorder. A venous blood gas is sufficient for these purposes. In our patient with advanced CKD, treatment was appropriately begun after a second low serum bicarbonate measurement, although without a confirmatory blood gas. The initial prescribed dose was higher than we would generally recommend, but was tolerated in this patient with well-controlled hypertension and no edema. The need for a high dose might have been predicted based on the inappropriately high urine pH indicative of a defect in urine acidification from sickle cell disease. The serum potassium normalized after starting alkali, which may have been partly been due to the kaliuretic effect of sodium bicarbonate.[34,39] Poor nutritional intake with advancing CKD also could have contributed, but this seems less likely given the increase in serum albumin and lack of weight loss. Fortunately, the patient did not experience gastrointestinal side effects and was able to continue treatment with long-term maintenance of a normal to low-normal serum bicarbonate.

We suggest using sodium bicarbonate to treat the chronic acidosis of CKD, usually starting with 650 mg twice daily (15.5 mEq/day of bicarbonate) and titrating upward based on the response. In a short-term intervention, each 0.1 mEq/kg/day higher dose increased serum bicarbonate by 0.33 mEq/L (95% confidence interval, 0.23 -0.43 mEq/L),[34] but the response may be greater over a period of months. If a poor response is observed and medication adherence is confirmed, renal bicarbonate wasting should be evaluated by measuring the urine pH. Baking soda is a cheaper alternative and especially useful for patients unable to tolerate the pill form (½ teaspoon dissolved in ½ cup water = 26.8 mEq bicarbonate). The most common side effect of sodium bicarbonate is bloating because of generation of carbon dioxide in the gastrointestinal tract. Sodium citrate is an alternative as citrate is rapidly metabolized to bicarbonate without produce bloating. However, it should be avoided in patients taking aluminum-containing antacids since citrate enhances intestinal aluminum absorption and increases the risk of aluminum toxicity.[40] Enteric-coated sodium bicarbonate may prevent dose dumping in the stomach, but there are no data demonstrating improved gastrointestinal tolerability with this formulation.

Phosphorus binders, such as calcium acetate or carbonate and sevelamer carbonate, also contribute small quantities of exogenous base. In contrast, sevelamer hydrochloride may exacerbate acidosis; the base form is therefore most commonly used. Medications that impair net acid excretion, such as potassium-sparing diuretics and non-steroidal anti-inflammatory agents, should be avoided whenever possible.

The importance of diet should also be considered. The typical Western diet, high in animal protein, has a large dietary acid load. Conversely, a diet rich in fruits and vegetables contains greater quantities of base precursors. Increased fruit and vegetable consumption increased serum bicarbonate (19.9±1.7 versus 19.3±1.9 mEq/L) in 76 patients with CKD stage 4 and serum total carbon dioxide <22 mEq/L, although less effectively than sodium bicarbonate. [41] As the medication arm received a relatively high dose of alkali (1.0 mEq/kg/day), the difference with fruits and vegetables might have been smaller had a lower dose been used. After 1 year, eGFR was not different between the 2 groups. Furthermore, fruits and vegetables reduced systolic blood pressure and did not induce hyperkalemia in this cohort, all of whom had serum potassium ≤4.6 mEq/L upon study entry. Therefore, in patients at low-risk for hyperkalemia, increased fruit and vegetable intake should be

routinely considered, with careful monitoring of the serum potassium early in the intervention.

The target serum bicarbonate with alkali therapy remains unclear. The goal set by KDOQI was opinion-based, and there are now intriguing data that a higher target may be preferable. The acid-inducing Western diet may increase tissue acidity without an observable change in plasma acid-base parameters.[42] Such increased interstitial acidity could produce the same sequelae as overt acidosis,[43] and beneficial effects of alkali might occur without a change in serum bicarbonate or pH. Thirty days of oral sodium bicarbonate in patients with mildly reduced eGFR reduced plasma endothelin-1 and aldosterone without a change in blood acid-base parameters. [44] In several positive studies of alkali in CKD patients, the mean serum bicarbonate at entry was 23-26 mEq/L, suggesting that even low-normal serum bicarbonate may be associated with deleterious effects.[34,38,44] Despite this encouraging data, it seems premature to target this degree of acidosis for correction with medication. However, increased fruit and vegetable intake seems a reasonable intervention given its numerous potential health benefits. Clearly, further studies are needed to better define the long-term effects of alkali therapy and to determine the efficacy of treating mild metabolic acidosis.

Base administration in the form of sodium salts is not without potential complications, including worsened hypertension, volume overload, and congestive heart failure. However, less sodium retention occurs with sodium bicarbonate compared to equimolar sodium chloride.[45] In a few studies, despite increased sodium intake, blood pressure remained similar between the sodium bicarbonate and control groups with no difference in antihypertensive medication requirements.[31,38] Although these studies are reassuring, their populations were pre-selected and often excluded patients with congestive heart failure and uncontrolled hypertension. Thus, in certain patients the addition of a diuretic or the increase in diuretic dose may be needed to avoid volume overload.

There is also the possibility of increased vascular calcification from systemic alkalinization. This potentially serious complication has not been well studied. In animal and *in vitro* studies, metabolic acidosis inhibited extraskeletal calcification.[46,47] Theoretically, alkali therapy could worsen vascular calcification, but no study has been performed in humans to test this effect. Finally, it is important to consider the pill burden and lesser side effects associated with alkali. Significant bloating or nausea may reduce appetite and food intake, which should be steadfastly avoided. The problems of high pill burden and polypharmacy have been well documented in the CKD population, and the impact of these additional pills should be considered on an individual basis.

In summary, chronic metabolic acidosis is associated with increased morbidity and mortality in patients with CKD. Existing evidence suggests alkali therapy might improve long-term outcomes in bone disease, muscle mass, and progression to ESRD. However, more data is needed to optimally guide treatment decisions. When initiating alkali therapy, one should consider the patient's comorbidities, the tolerability of therapy, and the target serum bicarbonate. The key teaching points are listed in Box 1.

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Box 1

Key Teaching Points

- Metabolic acidosis is a common complication of advanced CKD, especially with eGFR<30 ml/min/1.73 m^2.
- In patients with CKD, alkali therapy may decrease bone loss and protein degradation, increase muscle mass, and slow the progression of kidney disease. However, the optimal goal serum bicarbonate has not been defined.
- It is important to verify metabolic acidosis by a second measurement of serum bicarbonate and a venous blood gas before initiation of alkali therapy.
- Although alkali therapy is well-tolerated in most individuals, potential complications such as volume overload, congestive heart failure, and worsened hypertension need to be monitored.
- It is important to consider a patient's age, comorbidities, and pill burden when deciding to initiate alkali therapy.

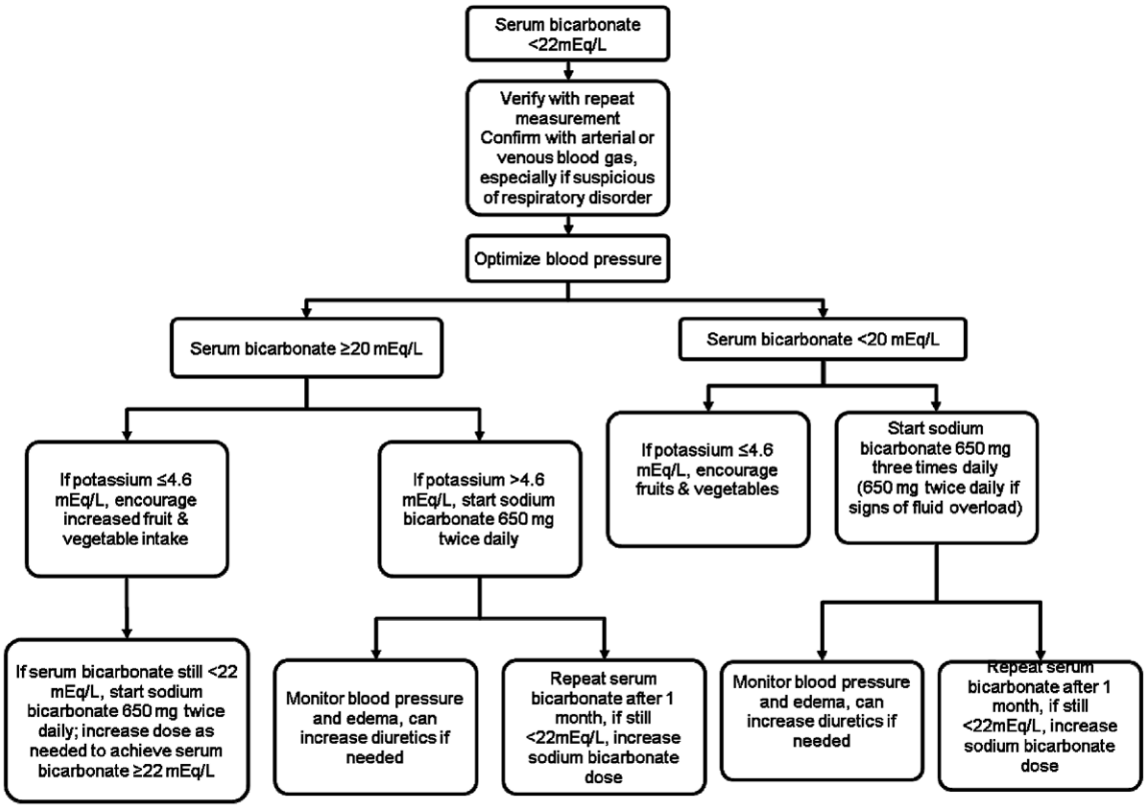

Figure 1. Algorithm for treating chronic metabolic acidosis in patients with chronic kidney disease

Baking soda (½ tsp = 26.8 mEq bicarbonate) can be substituted for sodium bicarbonate. Also consider sodium citrate if the patient does not tolerate sodium bicarbonate.

Table 1

Laboratory Data

	1 month prior	Day of the visit	3 months later	12 months later	16 months later
Serum chemistry					
Sodium (mEq/L)	140	139	141	140	141
Potassium (mEq/L)	5.8	5.4	4.6	4.4	4.9
Chloride (mEq/L)	111	110	108	101	106
Bicarbonate (mEq/L)	19	18	23	25	25
Urea nitrogen (mg/dL)	47	64	35	43	46
Creatinine (mg/dL)	3.4	3.3	3.8	4.9	4.2
eGFR (ml/min/1.73m^2)	23	23	20	15	18
Calcium (mg/dL)	10.1	9.4	10.0	11.0*	10.0
Phosphorus (mg/dL)	3.5	3.7	-	3.7	3.0
Anion gap (mEq/L)	10	11	10	14	10
Albumin (g/dL)	-	3.4	3.5	4.3	3.8
PTH (pg/mL)	309#	229	273	140	241
Urinalysis					
Specific gravity	1.013	-	-	1.015	-
pH	6.0	-	-	7.0	-

Note: Conversion factors for units: serum creatinine in mg/dL to μmol/L, ×84.4; serum urea nitrogen in mg/dL to mmol/L, ×0.357; serum calcium in mg/dL to mmol/L, ×0.2495; serum phosphorous in mg/dL to mmol/L, ×0.3229.

Abbreviations: eGFR, estimated glomerular filtration rate calculated using the 4-variable Modification of Diet in Renal Disease Study equation; PTH, parathyroid hormone.

*Hypercalcemia was secondary to exogenous activated vitamin D intake. Calcitriol was stopped.

#PTH measured two months prior to the day of the visit.

Table 2

Selected adverse effects of chronic metabolic acidosis in chronic kidney disease, and evidence for alkali therapy

	Adverse effect	Evidence for alkali therapy
Bone disease	Enhances bone resorption and impairs bone formation[48]	Reduces calcium losses in pre-dialysis CKD; has benefit in children with RTA[20], postmenopausal women with normal kidney function[21] and dialysis patients[22]
Protein metabolism	Decreases albumin synthesis, increases muscle proteolysis, and causes negative nitrogen balance[26]	Decreases protein degradation and may increase albumin concentration.[27,31] The data is conflicting in dialysis patients.[49,50]
Muscle mass	May contribute to muscle wasting[24,25]	May increase muscle mass and improve function.[31,34]
Kidney function	Could contribute to the progression of CKD	May slow the progression to kidney failure and development of ESRD[31,37,38]

Abbreviations: CKD, chronic kidney disease; RTA, renal tubular acidosis; ESRD, end stage renal disease