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Acid loading during treatment with sevelamer hydrochloride: Mechanisms and clinical implications

BARTON BREZINA, WAJEH Y. QUNIBI, and CHARLES R. NOLAN

University of Texas Health Sciences Center at San Antonio, San Antonio, Texas

Acid loading during treatment with sevelamer hydrochloride: Mechanisms and clinical implications. Short-term and long-term studies indicate that patients treated with sevelamer hydrochloride have lower serum bicarbonate levels than patients treated with calcium-containing phosphate binders. This observation has previously been attributed to withdrawal of a source of base with discontinuation of calcium carbonate or calcium acetate. However, understanding of the chemistry of sevelamer hydrochloride suggests at least three potential mechanisms whereby it might induce a dietary acid load. Moreover, preliminary results from an animal model demonstrate that treatment with sevelamer hydrochloride results in a fall in urine pH, as well as an increase in urinary ammonium and calcium excretion consistent with an increase in net acid excretion. Chronic metabolic acidosis in maintenance dialysis patients is associated with major systemic effects. It is independently associated with an increased risk of death in dialysis patients. Metabolic acidosis has both catabolic and antianabolic effects that may lead to a net negative nitrogen balance and total body protein balance. Metabolic acidosis also leads to physiochemical dissolution of bone and promotes cell-mediated bone resorption due to enhanced osteoclast activity and reduced osteoblast activity. It may also exacerbate secondary hyperparathyroidism and renal osteodystrophy. Given the long-term risks of chronic metabolic acidosis in maintenance dialysis patients, Kidney/Dialysis Outcome Quality Initiative (K/DOQI) guidelines have recently recommended maintaining predialysis serum levels of CO_2 above 22 mmol/L in order to improve bone histology, and to ameliorate excess protein catabolism.

Short-term and long-term studies have demonstrated that maintenance hemodialysis patients treated with sevelamer hydrochloride have significantly lower predialysis serum bicarbonate levels than patients treated with calcium-containing phosphate binders [1, 2]. In the recently published Calcium Acetate Renagel Evaluation (CARE study), hemodialysis patients were randomized to treatment with either calcium acetate or sevelamer hydrochloride [3]. Over the eight-week course of the study, sevelamer hydrochloride–treated patients had significantly lower serum bicarbonate levels than patients treated with calcium acetate (Fig. 1A). During weeks one to eight, mean serum bicarbonate levels ranged from 20.4 to 21.9 mEq/L with calcium acetate compared to 19.2 to 20.2 mEq/L with sevelamer hydrochloride. By the end of the eight weeks, the serum bicarbonate level increased to 21.0 ± 2.6 mEq/L (mean $\pm$ SD) with calcium acetate, while it decreased to 19.3 ± 2.7 with sevelamer hydrochloride. Moreover, sevelamer hydrochloride–treated patients were significantly more likely to have predialysis serum bicarbonate levels less than the National Kidney Foundation Kidney/Dialysis Outcome Quality Initiative (NFK K/DOQI) recommended guideline of 22 mEq/L (Fig. 1B).

Key words: sevelamer hydrochloride, metabolic acidosis, protein catabolism, renal osteodystrophy, acid loading.

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Potential mechanisms of acid loading during treatment with sevelamer hydrochloride

In the past, the finding of significantly lower serum bicarbonate levels in hemodialysis patients treated with sevelamer hydrochloride has been attributed to the fact that patients taking this non-calcium, non-aluminum phosphate binder are often withdrawn from an alkalinizing agent (carbonate or acetate) in the form of calcium-containing phosphate binders [4]. However, careful review of the chemistry of sevelamer hydrochloride suggests at least three potential mechanisms by which its use might lead to an increase in dietary mineral acid load. Sevelamer hydrochloride is a quaternary amine anion exchange resin that has been FDA-approved for use in dialysis patients as a dietary phosphate binder [5]. It is a nonabsorbed polymer chain with covalently linked amino groups, and 40% of these amino groups consist of amine hydrochloride. Overall, sevelamer contains 17% chloride by weight. The proposed phosphate-binding model for sevelamer hydrochloride is shown in Figure 2A. The quaternary amine resin acts as an anion exchanger whereby monovalent phosphate is bound (via ionic and hydrogen bonding) in exchange for release of the anion chloride. In this model, one molecule of hydrochloric acid is liberated for each molecule of phosphate bound in the gut.

Sevelamer hydrochloride may also exchange chloride for any other anion available in the gastrointestinal tract.

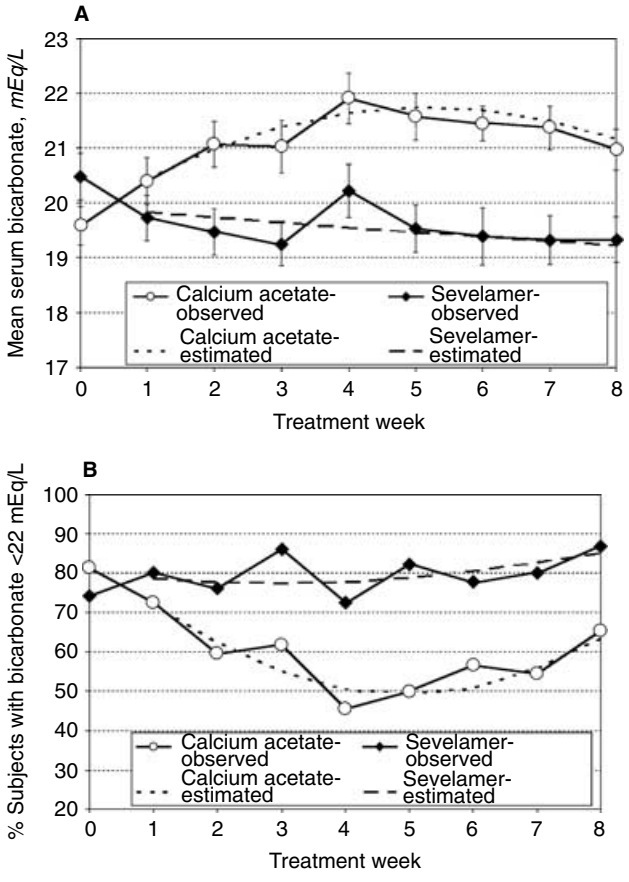

Fig. 1. Serum bicarbonate levels during treatment with calcium acetate or sevelamer hydrochloride in the CARE study. Mean serum bicarbonate levels at baseline and weekly during treatment in patients randomized to treatment with either calcium acetate (○) or sevelamer hydrochloride (◆). At baseline, serum bicarbonate was not significantly different between the calcium acetate and sevelamer hydrochloride groups (*P* value 0.11). However, during treatment mean serum bicarbonate levels were significantly lower in the sevelamer group than in the calcium acetate group (*P* value < 0.0001 by covariate-adjusted repeated measures regression) (*A*). Observed and model-estimated percent of subjects with serum bicarbonate <22 mEq/L by treatment group and week. Main treatment effect: *P* value < 0.0001. Reprinted with permission from Qunibi WY, Hootkins RE, McDowell LL, et al: Treatment of hyperphosphatemia in hemodialysis patients: The calcium acetate Renagel evaluation (CARE study). *Kidney Int* 65:1914–1926, 2004 (*B*).

For instance, in the small intestine, the local concentration of bicarbonate exceeds 100 to 120 mEq/L due to alkaline secretion from the pancreas, such that the chemical gradient would favor binding of bicarbonate in exchange for chloride. The elimination of carbonated sevelamer in the stool would result in gastrointestinal loss of bicarbonate in excess of chloride loss, thereby leading to metabolic acidosis via a mechanism similar that which occurs in the setting of chronic diarrhea (Fig. 2B).

Treatment of hemodialysis patients with sevelamer hydrochloride also results in a significant reduction in total and low-density lipoprotein (LDL) cholesterol [6]. Sevelamer hydrochloride is thought to exert its lipid-lowering effect by acting as a bile acid sequestrant with a mechanism of action similar to cholestyramine [7]. Binding of bile acids in exchange for chloride would also result in the net production of one molecule of HCl acid for every bile acid molecule bound (Fig. 2C). In this regard, treatment of patients with cholestyramine is known to result in a mineral acid load with development of metabolic acidosis and hypercalcuria [8–10]. The hypercalciuria is thought to be the result of chemical buffering of the acid load in the bone causing net efflux of calcium because treatment with sodium bicarbonate in an amount equal to the chloride content of administered cholestyramine prevents hypercalciuria [10].

Preliminary evidence from an animal model

Preliminary data from our laboratory indicate that normal rats treated with sevelamer hydrochloride develop a significant reduction in urine pH (Fig. 3A), a significant increase in urinary ammonium excretion (Fig. 3B), as well as a significant increase in urine calcium excretion (data not shown) [11]. These data support the concept that treatment with sevelamer hydrochloride results in a significant increase in dietary acid load.

Given that sevelamer hydrochloride contains 17% chloride by weight, and assuming complete exchange of chloride for phosphate, bicarbonate, or bile acids, each 800 mg tablet of sevelamer hydrochloride could theoretically lead to an acid load equivalent to 4 mEq HCl acid. Thus, dialysis patients treated with four 800 mg tablets of sevelamer hydrochloride thrice daily with meals as a phosphate binder might receive an additional dietary acid load approaching 46 mEq/day. These considerations suggest that a widespread shift from use of calcium-containing phosphate binders to sevelamer hydrochloride might result in an increase in the prevalence and severity of chronic metabolic acidosis in the hemodialysis population. Thus, it is important to consider the potential clinical implications of inadequately treated metabolic acidosis in dialysis patients [12].

RISKS OF CHRONIC METABOLIC ACIDOSIS IN DIALYSIS PATIENTS

Metabolic acidosis is common in patients with chronic kidney disease and results from reduced renal net acid excretion due to either defective renal ammoniagenesis or defective urine acidification. Dialysis therapy, as practiced today, is often inadequate to correct the metabolic acidosis associated with uremia. This has important clinical implications because metabolic acidosis, with serum bicarbonate below 17.5 mEq/L, has been independently associated with increased risk of death in dialysis patients [13].

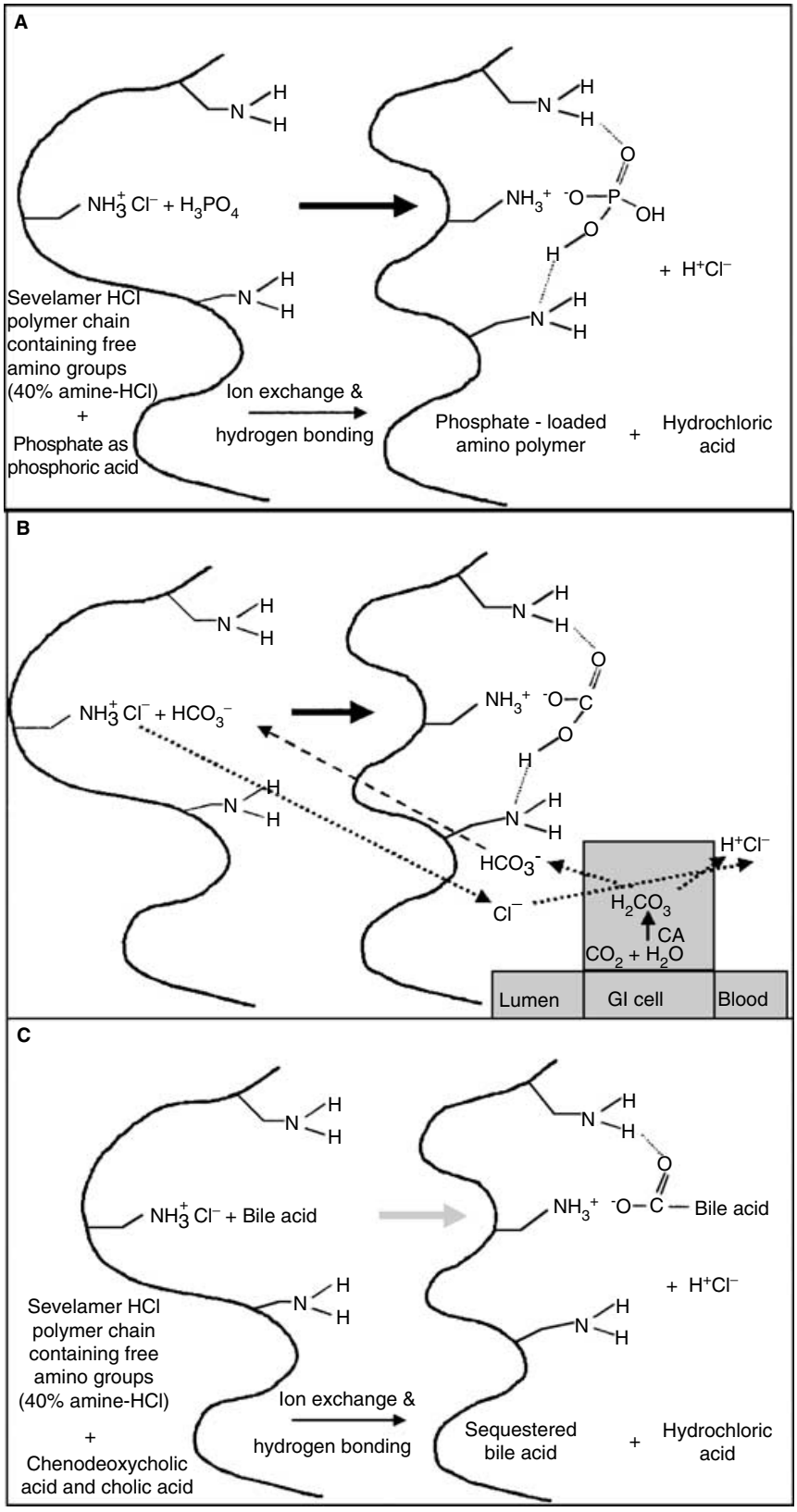

Fig. 2. Theoretical mechanisms of acid loading during treatment with sevelamer hydrochloride. Monovalent phosphate is bound to the sevelamer polymer via ionic and hydrogen-bonding interactions in exchange for release of the leaving anion chloride. For each phosphate molecule bound, one molecule of hydrochloride is produced (*A*). Exchange of chloride for bicarbonate in the small intestine. Loss of carbonated sevelamer in the stool leads to gastrointestinal losses of bicarbonate in excess of chloride. The net effect is production of excess HCl acid resulting in metabolic acidosis by a mechanism akin to development of nonanion gap metabolic acidosis in the setting of diarrhea (*B*). Sequestration of bile acids (cholic acid and chenodeoxycholic acid) by sevelamer in exchange for release of chloride. The net effect is the production of one HCl molecule for every molecule of bile acid bound (*C*). CA, carbonic anhydrase; GI, gastrointestinal.

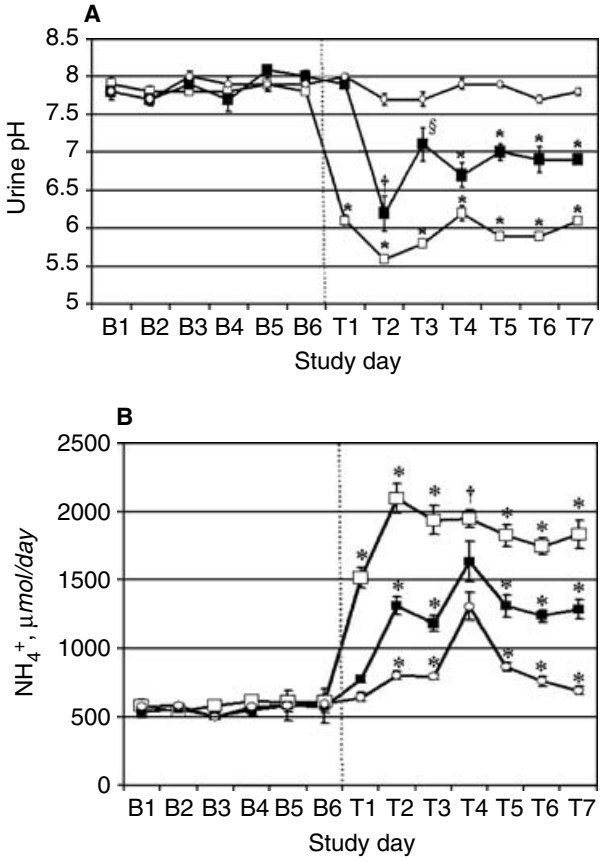

Fig. 3. Rat model demonstrating increased urinary net acid excretion during treatment with sevelamer hydrochloride. Normal rats ($N = 18$, 250 g male Sprague-Dawley) were placed on a regular diet for six days and then divided into three groups of six rats and treated with test agents admixed with diet for seven days as follows: group 1, sevelamer hydrochloride: 1 g/day containing 5 mmol/L chloride (closed squares); group 2, HCl acid: 5 mmol/day (open squares); and group 3, sodium chloride: 5 mmol/day (open circles). Rats were housed in metabolic cages to measure 24-hour urine for pH (*A*) and NH_4^+ excretion (µmol/day; measured by ion specific electrode) (*B*). $^*P < 0.05$ vs. baseline and other treatment groups, †$P < 0.05$ vs. baseline and NaCl treatment group, §$P < 0.05$ vs. baseline and HCl acid treatment groups.

Protein catabolic effects of chronic metabolic acidosis

In normal individuals and patients with chronic kidney disease, metabolic acidosis leads to negative nitrogen balance [14, 15]. Both animal and human studies indicate that metabolic acidosis is associated with proteolysis, and that correction of acidosis, in turn, results in a decrease in protein degradation. Rats treated with ammonium chloride demonstrate elevated protein degradation and amino acid oxidation, which can be prevented by addition of sodium bicarbonate to the diet [16, 17]. Acidosis has been shown to induce catabolism of essential amino acids by up-regulating the activity of an enzyme called branched-chain ketoacid dehydrogenase [18, 19]. Many studies in humans with chronic kidney disease have demonstrated that metabolic acidosis promotes proteolysis [20–23]. The enhanced muscle protein catabolism in

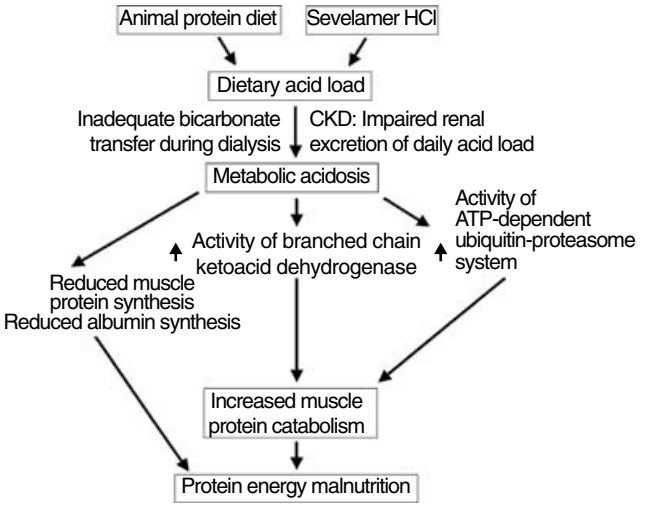

Fig. 4. Effects of metabolic acidosis on protein metabolism.

metabolic acidosis appears to be related to an increase in the activity of the ATP-dependent ubiquitin-proteosome pathway for protein degradation [24, 25].

Metabolic acidosis may also have antianabolic effects. Ammonium chloride–induced metabolic acidosis in normal subjects is associated with a significant reduction in the fractional synthetic rate of muscle protein [26], as well as a reduction in the fractional synthetic rate for albumin [15]. Metabolic acidosis may also cause a state of insulin resistance. In euglycemic clamp studies, ammonium chloride–induced metabolic acidosis leads to impaired glucose metabolism as the result of reduced tissue sensitivity to insulin [27]. Insulin resistance may in turn have a detrimental effect on muscle protein metabolism. The detrimental effects of metabolic acidosis on nitrogen balance and protein metabolism are outlined in Figure 4.

Adverse effects of metabolic acidosis on bone disease

In patients with chronic kidney disease and patients with end-stage renal disease on maintenance hemodialysis, the reduction in net acid excretion may lead to a net positive proton balance [28]. The accumulated acid is buffered in the bone such that in the setting of uncorrected metabolic acidosis there is ongoing consumption of bone buffers with dissolution of bone and release of calcium and phosphorus [29, 30]. In vitro data demonstrate that metabolic acidosis is associated with net calcium efflux from bone. This net calcium efflux is due in part to physiochemical dissolution of bone during the process of proton buffering [31]. However, acidosis may also lead to enhanced cell-mediated bone resorption. Acidosis is known to stimulate osteoclast function and inhibit osteoblast function with a net effect favoring enhanced bone resorption [32, 33]. In patients with chronic kidney disease not treated with dialysis, severe metabolic

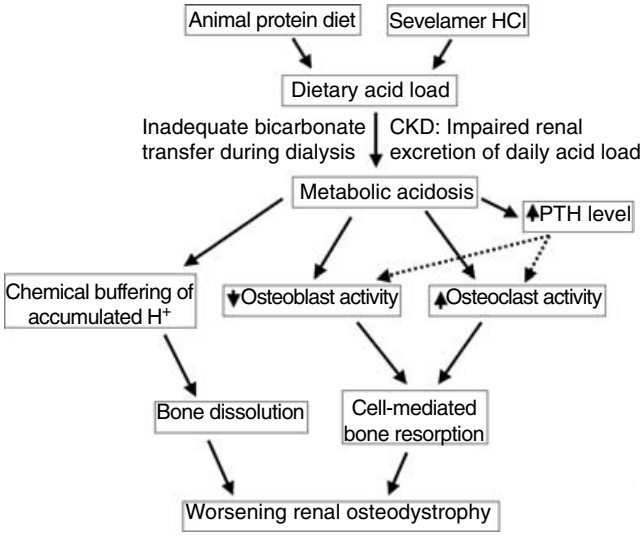

Fig. 5. Effects of metabolic acidosis on bone disease.

acidosis is associated with impaired bone mineralization and an increased incidence of osteomalacia [30, 34–36]. Moreover, bone mineralization rate may increase following correction of metabolic acidosis in these patients [30].

Metabolic acidosis may also indirectly affect bone disease via changes in parathyroid hormone (PTH). In nondialyzed patients with chronic kidney disease, there is an inverse relationship between serum bicarbonate and serum PTH levels [37]. In uremic patients on maintenance hemodialysis, metabolic acidosis is also associated with increased PTH levels [38]. Moreover, PTH levels decline after correction of metabolic acidosis [39]. Correction of metabolic acidosis may thus retard the progression of dialysis osteodystrophy [38]. It should also be noted that metabolic acidosis and PTH may have synergistic effects on bone such that in the presence of metabolic acidosis, PTH stimulates substantially more net efflux of calcium from bone, greater enhancement of osteoclast activity, and stronger inhibition of osteoblast activity [40–41]. Thus, available evidence indicates that metabolic acidosis may lead to worsening of secondary hyperparathyroidism and renal osteodystrophy (Fig. 5).

TREATMENT OF METABOLIC ACIDOSIS IN PATIENTS ON MAINTENANCE HEMODIALYSIS

There is some evidence in patients on maintenance hemodialysis that treatment of metabolic acidosis may result in amelioration or improvement in renal osteodystrophy. One study in 21 patients on maintenance hemodialysis found that a group of patients with acidosis (total CO_2 = 15 mmol/L) had progression of secondary hyperparathyroidism both biochemically and on bone biopsy compared with patients in the control group (total CO_2 = 24 mmol/L) [38]. In a cross-sectional study of 76 patients with chronic kidney disease not yet on dialysis, those with normal transiliac bone biopsy had a serum bicarbonate level of 23 mmol/L, while those patients with either mild or advance mixed renal osteodystrophy had serum bicarbonate levels less than 20 mmol/L [42]. Furthermore, evidence suggests that the absence of metabolic acidosis renders the therapy of osteodystrophy with vitamin D metabolites more effective [36]. In children with renal tubular acidosis, normalization of serum bicarbonate is one component of successful return of normal growth parameters [43].

The recently published National Kidney Foundation K/DOQI clinical practice guidelines for Bone Metabolism and Disease in Chronic Kidney Disease recommend measurement and monitoring of the serum levels of total CO_2 in patients with chronic kidney disease stages 3, 4, and 5, and in patients on maintenance hemodialysis [44]. Therapeutic maneuvers to keep predialysis levels of total CO_2 above 22 mmol/L are recommended both to promote improvement in bone histology [36] and to ameliorate excess protein catabolism [45]. Increasing the bicarbonate level in the dialysate is one therapeutic option. However, evidence indicates that in patients treated with sevelamer hydrochloride, even increasing the dialysate bicarbonate level to 40 mEq/L may be inadequate to achieve K/DOQI guidelines for total CO_2. In one cross-sectional study of 30 patients on maintenance hemodialysis treated with sevelamer hydrochloride for at least one year (mean 23 months, range 13 to 40 months), despite treatment with standard dialysis bicarbonate of 40 mEq/L, mean serum bicarbonate was 18.6 $\pm$ 2.7, and 77% of these patients had serum bicarbonate less than 20 mEq/L [abstract; Ciampi MA et al, *J Am Soc Nephrol* 13:586A, 2002]. In contrast, in patients treated with calcium-containing phosphate binders the mean serum bicarbonate was 20.3 $\pm$ 1.8 mEq/L, and only 36% of patients had bicarbonate levels less than 20 mEq/L.

Thus, to achieve and maintain the goal total CO_2 above 22 mmol/L in patients treated with sevelamer hydrochloride, it may be necessary to provide supplemental alkali salts such as sodium bicarbonate [44]. It should also be noted that treatment with supplemental sodium bicarbonate might reduce the phosphate-binding efficacy of sevelamer hydrochloride because the exogenous bicarbonate will compete with dietary phosphate for binding to the anion exchange resin. It is also important to remember that use of exogenous alkali salts containing citrate may increase the absorption of dietary aluminum [46], thereby increasing the risk of aluminum-induced bone disease and encephalopathy in patients with chronic kidney disease. For this reason, alkalinizing therapy with sodium citrate or other citrate alkali salts is contraindicated in patients with advanced chronic kidney disease or those with ESRD on maintenance hemodialysis.

CONCLUSION

Hemodialysis patients treated with sevelamer hydrochloride consistently have lower serum bicarbonate levels than patients treated with calcium-containing phosphate binders. This observation is unlikely to be related solely to withdrawal of a source of base such as acetate or carbonate. It may also be caused by an increased dietary acid load during treatment with sevelamer hydrochloride. This notion is supported by preliminary results from our laboratory, in which rats treated with sevelamer hydrochloride had a fall in urine pH, as well as an increase in urinary ammonium and calcium excretion consistent with an increase in net acid excretion. Chronic metabolic acidosis in maintenance dialysis patients is associated with major systemic effects, including worsening of secondary hyperparathyroidism, net negative nitrogen and total body protein balance, and increased risk of death. For that reason, the long-term risks of worsening metabolic acidosis in hemodialysis patients treated with sevelamer hydrochloride clearly deserve further study. In the meanwhile, it is possible that reformulation of sevelamer hydrochloride may be necessary so that this phosphate-binding anion exchange resin contains less chloride and more acetate or carbonate.

Reprint requests to Charles R. Nolan, M.D., Professor of Medicine & Surgery, Medical Director, Kidney & Pancreas Transplantation, 7703 Floyd Curl Drive, San Antonio, TX 78229–3900.
E-mail: nolan@uthscsa.edu

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