Veverimer: an advance in base therapy for metabolic acidosis

Clayton Brady[1], Elie R. Chemaly[2], James W. Lohr[2], Mark D. Parker[1]

[1]Department of Physiology and Biophysics, [2]Department of Medicine, Division of Nephrology, Jacobs School of Medicine and Biomedical Sciences, The State University of New York: University at Buffalo, Buffalo, NY, USA

Correspondence to: Mark D. Parker. Department of Physiology and Biophysics, Jacobs School of Medicine and Biomedical Sciences, The State University of New York: University at Buffalo, 955 Main Street, Buffalo, NY 14203, USA. Email: parker28@buffalo.edu.

Comment on: Wesson DE, Mathur V, Tangri N, *et al.* Long-term safety and efficacy of veverimer in patients with metabolic acidosis in chronic kidney disease: a multicentre, randomised, blinded, placebo-controlled, 40-week extension. Lancet 2019;394:396-406.

Submitted Mar 24, 2020. Accepted for publication Apr 22, 2020.

doi: 10.21037/atm-20-2827

View this article at: http://dx.doi.org/10.21037/atm-20-2827

Introduction

Metabolic acidosis (MAc) is defined as a reduction in plasma bicarbonate concentration {[HCO_3^-] <22 mEq/L} that is not a compensatory response to respiratory alkalosis (1). MAc is one of the earliest complications of chronic kidney disease (CKD), and increases in prevalence with declining glomerular filtration rate (1). Overall, MAc occurs in 15% of all CKD patients, and in up to 37% of patients with stage 4 CKD (2). The treatment of MAc in CKD (CKD-MAc) can be challenging because of the need to introduce HCO_3^- without surplus counterions, such as sodium (Na^+), which can exacerbate fluid overloaded states, or potassium (K^+), which can precipitate hyperkalemia (1). Moreover, the introduction of excess alkali can itself be harmful (1).

To avoid the unwanted effects associated with alkali therapy, the first-in-class pharmaceutical, veverimer, has been developed. Veverimer is an acid-binding polymer that raises plasma [HCO_3^-] without introducing unwanted cations. In the June 2019 edition of *Lancet*, Wesson *et al.* presented the results of a randomized placebo-controlled trial that examined the safety and efficacy of veverimer in the treatment of CKD-MAc (3). In this commentary, we review those findings in the context of the underlying basic science and prevailing treatment strategies.

HCO_3^- and the kidneys

The HCO_3^- buffering-system is essential for maintaining plasma pH within normal range (pH 7.35–7.45) in the face of the daily load of dietary and endogenously-produced acids.

$$HCO_3^- + H^+ \rightleftharpoons CO_2 + H_2O$$

The consumption of HCO_3^- by the daily acid-load requires the generation of equimolar amounts of HCO_3^- in order to maintain an adequate HCO_3^- pool [normal plasma (HCO_3^-) = 23–30 mEq/L] (1) to preserve the plasma's pH and buffer capacity. HCO_3^- replenishment is predominantly accomplished by epithelial cells in the proximal tubules of the kidneys by a series of metabolic reactions that result in the production of H^+ or NH_4^+ (which are excreted in the urine) and HCO_3^- [which is absorbed into circulation: reviewed in (4)]. Failure of the kidneys to match the daily acid-load with an equivalent amount of HCO_3^- production results in MAc. The pathogenesis of CKD-MAc is a decrease in renal function, which impairs the renal production of HCO_3^- (1). CKD-MAc has been implicated in the development of osteopenia and osteoporosis, decreased muscle mass, decreased insulin release and sensitivity, vascular endothelial dysfunction, progression of CKD to end-stage renal disease (ESRD), cardiovascular disease, and an overall increased risk of death [*Figure 1* and see reference (5)]. Thus, the continued evaluation of HCO_3^- status in CKD patients is essential and findings of CKD-MAc should prompt initiation of treatment. However, therapy is often limited or even impossible due to insufficient treatment options and the prevalence of comorbidities, underscoring the need for the development of new therapies for CKD-MAc.

Prevailing alkali therapies

Dietary management is often a first-line treatment to

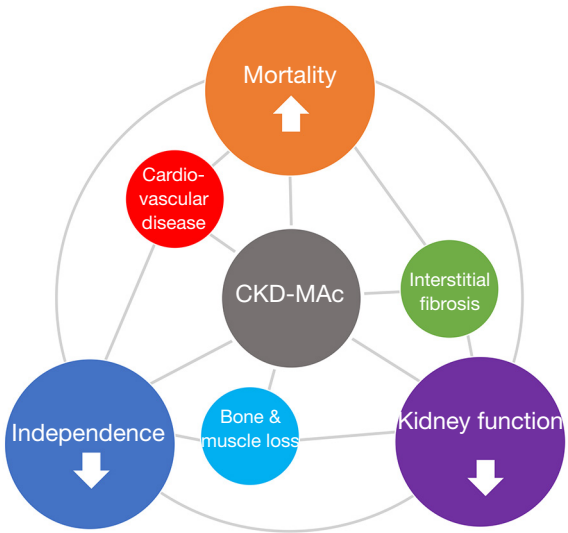

Figure 1 A network of pathologies associated with CKD-MAc. The effects of CKD-MAc are multifaceted and incompletely understood. Acid retention can trigger inflammatory mechanisms (e.g., complement activation and cytokine release), which leads to kidney interstitial fibrosis and worsening of CKD. Chronic low pH decreases bone mineralization and increases muscle protein metabolism leading to increased fragility in patients. Activation of hormonal mechanisms (e.g., endothelin and angiotensin II release) can also damage the kidney, as well as cause fluid retention and atherosclerotic plaque development that can lead to development of cardiovascular disease. Evidence that high (HCO_3^-) may also be associated with cardiovascular disease adds to the complexity of potential treatment guidelines. Overall, worsening CKD to the point of needing dialysis and the progression of co-morbid conditions such as fragility and cardiovascular disease, together decrease independence and contribute directly to mortality. See reference (5) for a more thorough review.

restore plasma pH, with patients instructed to eat more fruits and vegetables (which contain a greater proportion of base-producing amino acids) and decrease their intake of animal protein (which contains a greater proportion of acid-producing amino acids) (1). However, many fruits and vegetables are also rich in K^+ and therefore such diets require careful management in CKD patients due to the increased risk of hyperkalemia (1). The current standard treatment recommendation for CKD-MAc, as defined in the Kidney Disease Improving Global Outcomes guidelines, is to begin oral $NaHCO_3$ (baking soda) administration in any patient with serum [HCO_3^-] <22 mEq/L (6). Orally-dosed HCO_3^- neutralizes gastric acid to stimulate hydrochloric acid (HCl) secretion by parietal cells and enhance delivery of HCO_3^- into the blood (*Figure 2*), mimicking a postprandial alkaline tide. The grade given to this recommendation is 2B; with the implication that the quality of evidence for the recommendation is "moderate" and that "different choices will be appropriate for different patients" (6). However, the use of $NaHCO_3$ therapy is off label for the chronic treatment of MAc in the USA (3). As mentioned, a major complication of oral HCO_3^- administration is that it necessarily includes a counterion (Na^+ or K^+), which may require dietary management to avoid Na^+-related fluid retention or hyperkalemia (8). Another complication is that the reaction between HCO_3^- and HCl generates CO_2, which can cause bloating and stomach discomfort, often limiting patient compliance (8). While exceedingly rare, in severe cases the pressure caused by CO_2 build-up can result in gastric rupture (9). However, both vegetarian diets and oral HCO_3^- dosing are appealing in their simplicity and availability and can be feasible options, given appropriate dietary counseling (10,11). A third form of treatment is citrate-based therapy (oral dosing of Na^+- or K^+-citrate), which increases plasma HCO_3^- through conversion of citrate to HCO_3^- in the liver and, in general, has a milder gastrointestinal side-effect profile than HCO_3^--based therapy (1). A caution to investigations implementing any form of alkaline therapy is that too much HCO_3^- can also be harmful (1). For example, the association between [HCO_3^-] and cardiovascular disease, which accounts for the majority of deaths in the CKD population (12),

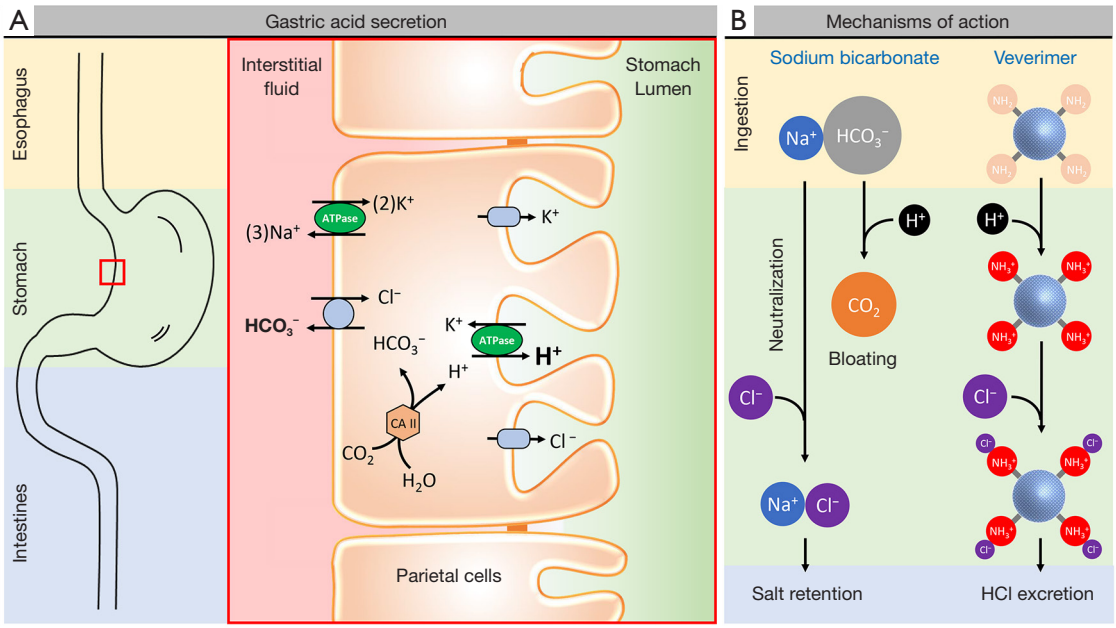

Figure 2 The mechanism of action of veverimer versus sodium bicarbonate in the treatment of MAc. (A) Parietal cells secrete H^+ across their apical membranes using a H^+/K^+-ATPase. Intracellular H^+ are replaced by the action of carbonic anhydrase II (CAII), which also generates HCO_3^- that must be absorbed into the blood to maintain parietal cell pH. This is achieved by the exchange of intracellular HCO_3^- for interstitial Cl^-, a process mediated by the anion exchange protein AE2. (B) HCl in the stomach lumen may be neutralized by orally administered $NaHCO_3$ with the production of unwanted NaCl and CO_2. Veverimer sequesters HCl in the stomach lumen, removing H^+ without generating these byproducts. The effectiveness of veverimer is such that it temporarily causes gastric pH to rise between 1.5–3.0 units (7). The replacement of gastric acid that was neutralized by these treatments results in the enhanced production of HCO_3^- by parietal cells, mimicking a postprandial alkaline tide.

is 'U-shaped'; too much HCO_3^- can be as detrimental as too little (13,14).

The action and efficacy of veverimer

Veverimer (also known as TRC101) is an orally-administered, non-absorbed, binder of HCl that takes the form of ~100 µm diameter beads composed of crosslinked, high-molecular-weight polyamines (15). Veverimer acts by sequestering HCl from the stomach which, like the action of orally-dosed $NaHCO_3$, stimulates gastric HCl secretion and enhances delivery of HCO_3^- into the blood (*Figure 2*). The HCl-bound veverimer is ultimately excreted in the feces. Importantly, unlike orally dosed $NaHCO_3$, veverimer does not introduce unwanted absorbable cations into the gastrointestinal tract, nor does its action generate CO_2 (7).

A side-by-side comparison of veverimer and $NaHCO_3$ has yet to be performed but, in Lancet article that is the subject of this commentary, Wesson *et al.* report the results of a randomized, phase-3 clinical trial that examined the safety and efficacy of veverimer versus a placebo in the treatment of CKD-MAc over a 52-week period (3). This was a 40-week extension of a 12-week parent study (16). Of the 196 CKD patients enrolled in this extension, 114 received veverimer orally and 82 received an oral placebo (microcrystalline cellulose, a common bulking-agent in tablets that has no known or anticipated effects on acid-base balance). The study's primary endpoint was safety (incidence and severity of adverse events), with secondary endpoints related to the efficacy of veverimer, such as blood $[HCO_3^-]$ and physical functioning. Over the original 12-week parent study some patients were kept on a stable dose of oral alkali therapy as part of their 'baseline'; this therapy was kept constant and no other $[HCO_3^-]$ raising therapies were allowed to be initiated. Before entering the 40-week extension, patients with $[HCO_3^-] \geq 22$ mEq/L were taken off any prior oral alkali therapy, however if their $[HCO_3^-]$ then fell <22 mEq/L, and could not be corrected

with maximal dosing of the study drug, oral alkali therapy was reinstated at the patient's week-12 dosage. There were no specific dietary restrictions, however all patients received dietary counseling.

In this cohort of patients, with moderate to severe CKD and baseline HCO_3^- concentrations of 14–20 mEq/L, veverimer performed well compared to placebo both in terms of efficacy and safety. In regard to efficacy, more patients on veverimer than placebo had an increase in blood [HCO_3^-] by at least 4 mEq/L above baseline or to within target range (22–29 mEq/L) at week 52, with subgroup analysis suggesting that these effects are most pronounced in individuals over 65 years or in females. The mean blood [HCO_3^-] of the veverimer treated group was higher than placebo at all timepoints starting at week 1, was maximized by 4 weeks of treatment, and was sustained over the trial period. Furthermore, patients taking veverimer reported increased physical functioning over the 52 weeks, a finding supported by improvements in physical-testing metrics such as 'time from chair to standing'. In regard to safety, the authors report that veverimer was well tolerated with no significant difference from placebo in occurrence of adverse effects. Gastrointestinal events were the most commonly reported adverse effects in both groups, but were mild or moderate and none required treatment or resulted in discontinuation from the study.

Can veverimer delay the progression of CKD?

Whether treatment of CKD-MAc with veverimer slows the progression of CKD is a major unanswered question. The study by Wesson *et al.* was not powered to assess the effect of veverimer on CKD progression (the sample size of the 40-week extension was bounded by the number of eligible patients who followed through from the parent study); the primary endpoint of the extension was safety. However, in consideration of the entire 52-week study (including those 21 individuals who discontinued during the parent trial or who did not continue into the extension phase), the authors do report a statistically significant improvement in their composite endpoint (number of deaths, need for renal replacement therapy, or a decline in the estimated glomerular filtration rate, eGFR, of >50%) in the veverimer-treated group (4%) compared to placebo (12%).

This improvement in the composite endpoint in the veverimer-treated group is similar to that achieved by oral $NaHCO_3$ dosing in the 'Use of HCO_3^- in Renal Insufficiency' (UBI) study, which was published just two months later (11). The UBI study was an open-label, controlled trial, investigating the effect of $NaHCO_3$-administration on the preservation of kidney function, with secondary endpoints of time to renal replacement therapy and all-cause mortality. The study enrolled 740 total patients, making it the largest to date examining $NaHCO_3$ administration in CKD. Using a similar target [HCO_3^-] range and achieving a similar efficacy in reaching that target compared to the veverimer trial, the UBI study reports a significant reduction in risk of their composite endpoint (death, need for dialysis, or doubling of creatinine). This might be taken as a promising indicator for an ongoing trial that is specifically designed to investigate the effect of veverimer versus placebo on CKD progression (ClinicalTrials.gov, Identifier: NCT03710291), which is due for completion in 2022.

A significant advantage of the veverimer study is the widening of inclusion criteria for hypertension and heart-failure to systolic blood pressure <170 mmHg and New York Heart Association (NYHA) Functional Classification I–III heart failure (including individuals with slight or marked limitation of physical activity), respectively. These patients are often sensitive to Na^+, and thus had been excluded in previous studies examining effects Na^+-based alkali therapies (17-19). For example, the UBI study (11) only included patients with systolic blood pressure <150 mmHg and NYHA Functional Classification I–II heart failure (excluding individuals with marked limitation of physical activity), similar to the earlier smaller studies examining $NaHCO_3$ administration (17-19). Thus, as Wesson *et al.* point out, the veverimer trial was able to recruit a cohort that was probably a more accurate representation of the general CKD population (3).

On the other hand, no past or present veverimer trial allows the direct comparison of the efficacy of veverimer to that of traditional therapies such as $NaHCO_3$ in delaying the progression of CKD or improving other clinical outcomes. Considering the simplicity and benefit of $NaHCO_3$ supplementation demonstrated recently in the UBI study, in conjunction with the benefit of veverimer demonstrated by Wesson *et al.*, a rigorous head-to-head comparison between $NaHCO_3$ and veverimer would provide optimal guidance to the clinician. The ideal study would include an epidemiologically diverse patient population and would be powered to assess the long-term safety and efficacy of veverimer and $NaHCO_3$ compared to placebo in delaying the progression of CKD towards end-stage renal disease.

Future studies would also address the benefit of alkaline therapy in a broader range of renal dysfunction, in contrast to the study by Wesson *et al.* which included patients with eGFR ranging between 20 and 40 mL/min with relatively moderate albuminuria (3).

However, the treatments need not be mutually exclusive; indeed some veverimer trial subjects were allowed to continue alkali therapy if a maximum dose of veverimer was not effective at normalizing [HCO_3^-]. One might envision a situation in which traditional alkali therapies could be maintained as a simple intervention in early stages of CKD in individuals who tolerate it well, whereas veverimer may be most valuable later in disease progression when the additional load of Na^+ or K^+ is contraindicated. Patients may qualify for combination therapy in advanced disease: concerns of fluid overload could be mitigated by the use of diuretics.

Beyond CKD-MAc

For healthy older adults, a study investigating the association between [HCO_3^-] and mortality, demonstrated a 22% higher risk of death in patients with [HCO_3^-] <23 mEq/L (20). Importantly, this risk was independent of pH {i.e., low [HCO_3^-] could be due to MAc or respiratory alkalosis}, suggesting that [HCO_3^-] itself is a vital parameter independent of its consequence for pH. Thus, there are conditions besides CKD-MAc in which drugs such as veverimer could be valuable to raise [HCO_3^-]. It will be interesting to learn from future studies how the efficacy of veverimer compares to that of traditional alkali therapies in ameliorating the detrimental effects of low [HCO_3^-].

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned and reviewed by the Section Editor Dr. Cheng Yuan (Zhongnan Hospital, Wuhan University, China).

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/atm-20-2827). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1. Raphael KL. Metabolic acidosis in CKD: Core Curriculum 2019. Am J Kidney Dis 2019;74:263-75.
2. Raphael KL. Metabolic acidosis and subclinical metabolic acidosis in CKD. J Am Soc Nephrol 2018;29:376-82.
3. Wesson DE, Mathur V, Tangri N, et al. Long-term safety and efficacy of veverimer in patients with metabolic acidosis in chronic kidney disease: a multicentre, randomised, blinded, placebo-controlled, 40-week extension. Lancet 2019;394:396-406.
4. Weiner ID, Verlander JW. Recent advances in understanding renal ammonia metabolism and transport: Curr Opin Nephrol Hypertens 2016;25:436-43.
5. Kraut JA, Madias NE. Adverse effects of the metabolic acidosis of chronic kidney aisease. Adv Chronic Kidney Dis 2017;24:289-97.
6. KDIGO 2012 Clinical practice guideline for the evaluation and management of chronic kidney disease. Kidny Int Suppl 2013;3:1-150.
7. Tricida 2018 Annual Report and Proxy. Tricida. Available online: https://ir.tricida.com/financial-information/annual-reports
8. Bushinsky DA. Tolerance to sodium in patients with CKD-induced metabolic acidosis: Does the accompanying anion matter? Am J Kidney Dis 2019;73:858-65.
9. Vásquez A, Domínguez C, Perdomo CF. Spontaneous gastric rupture after sodium bicarbonate consumption: A case report. Radiography 2017;23:e62-4.
10. Goraya N, Simoni J, Jo CH, et al. A comparison of treating metabolic acidosis in CKD stage 4 hypertensive kidney disease with fruits and vegetables or sodium bicarbonate. Clin J Am Soc Nephrol 2013;8:371-81.
11. Di Iorio BR, Bellasi A, Raphael KL, et al. Treatment

of metabolic acidosis with sodium bicarbonate delays progression of chronic kidney disease: the UBI Study. J Nephrol 2019;32:989-1001.
12. Go AS, Chertow GM, Fan D, et al. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. N Engl J Med 2004;351:1296-305.
13. Dobre M, Yang W, Chen J, et al. Association of serum bicarbonate with risk of renal and cardiovascular outcomes in CKD: A report From the Chronic Renal Insufficiency Cohort (CRIC) study. Am J Kidney Dis 2013;62:670-8.
14. Dobre M, Roy J, Tao K, et al. Serum bicarbonate and structural and functional cardiac abnormalities in chronic kidney disease - A report from the Chronic Renal Insufficiency Cohort Study. Am J Nephrol 2016;43:411-20.
15. Bushinsky DA, Hostetter T, Klaerner G, et al. Randomized, controlled trial of TRC101 to increase serum bicarbonate in patients with CKD. Clin J Am Soc Nephrol 2018;13:26-35.
16. Wesson DE, Mathur V, Tangri N, et al. Veverimer versus placebo in patients with metabolic acidosis associated with chronic kidney disease: a multicentre, randomised, double-blind, controlled, phase 3 trial. Lancet 2019;393:1417-27.
17. de Brito-Ashurst I, Varagunam M, Raftery MJ, et al. Bicarbonate supplementation slows progression of CKD and improves nutritional status. J Am Soc Nephrol JASN 2009;20:2075-84.
18. Goraya N, Simoni J, Jo CH, et al. Treatment of metabolic acidosis in patients with stage 3 chronic kidney disease with fruits and vegetables or oral bicarbonate reduces urine angiotensinogen and preserves glomerular filtration rate. Kidney Int 2014;86:1031-8.
19. Phisitkul S, Khanna A, Simoni J, et al. Amelioration of metabolic acidosis in patients with low GFR reduced kidney endothelin production and kidney injury, and better preserved GFR. Kidney Int 2010;77:617-23.
20. Raphael KL, Murphy RA, Shlipak MG, et al. Bicarbonate concentration, acid-base status, and mortality in the health, aging, and body composition study. Clin J Am Soc Nephrol 2016;11:308-16.

Cite this article as: Brady C, Chemaly ER, Lohr JW, Parker MD. Veverimer: an advance in base therapy for metabolic acidosis. Ann Transl Med 2020;8(20):1331. doi: 10.21037/atm-20-2827

