Veverimer: an advance in base therapy for metabolic acidosis

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Introduction

Metabolic acidosis (MAc) is defined as a reduction in plasma bicarbonate concentration ([HCO₃⁻] < 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 HCO₃⁻ 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 [HCO₃⁻] 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.

HCO₃⁻ and the kidneys

The HCO₃⁻ 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.

\[ \text{HCO}_3^- + H^+ \rightleftharpoons CO_3 + H_2O \]

The consumption of HCO₃⁻ by the daily acid-load requires the generation of equimolar amounts of HCO₃⁻ in order to maintain an adequate HCO₃⁻ pool [normal plasma (HCO₃⁻) = 23–30 mEq/L] (1) to preserve the plasma’s pH and buffer capacity. HCO₃⁻ 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 NH₄⁺ (which are excreted in the urine) and HCO₃⁻ [which is absorbed into circulation: reviewed in (4)]. Failure of the kidneys to match the daily acid-load with an equivalent amount of HCO₃⁻ production results in MAc. The pathogenesis of CKD-MAc is a decrease in renal function, which impairs the renal production of HCO₃⁻ (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 HCO₃⁻ 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
Prevailing alkali therapies

Dietary management is often a first-line treatment to 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 (7). 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 (7). While exceedingly rare, in severe cases the pressure caused by CO\(_2\) build-up can result in gastric rupture (8). 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 (9,10). 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 (11), is 'U-shaped'; too much HCO$_3^-$ can be as detrimental as too little (12,13).

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 (14). 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$_2$ (15).

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 \([\text{HCO}_3^-]\) raising therapies were allowed to be initiated. Before entering the 40-week extension, patients with \([\text{HCO}_3^-] \geq 22\text{ mEq/L}\) were taken off any prior oral alkali therapy, however if their \([\text{HCO}_3^-]\) 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 \([\text{HCO}_3^-]\) 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 \([\text{HCO}_3^-]\) 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 \([\text{HCO}_3^-]\) 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 NaHCO₃ dosing in the ‘Use of HCO₃⁻ in Renal Insufficiency’ (UBI) study, which was published just two months later (10). The UBI study was an open-label, controlled trial, investigating the effect of NaHCO₃ 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 NaHCO₃ administration in CKD. Using a similar target \([\text{HCO}_3^-]\) 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 (10) 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 NaHCO₃ 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 NaHCO₃ in delaying the progression of CKD or improving other clinical outcomes. Considering the simplicity and benefit of NaHCO₃ 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 NaHCO₃ 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$_3^-$].

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**Footnote**

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