New Frontiers in Treating Uremic Metabolic Acidosis

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Metabolic acidosis is a frequent complication of CKD. Metabolic acidosis is caused by the damaged kidney's inability to excrete acid due to the reduction in kidney mass. Metabolic acidosis has been associated with bone disease, muscle dysfunction, and kidney damage (1–3). Current practice guidelines recommend treatment with alkali therapy when the serum bicarbonate level decreases to <22 mEq/L to prevent associated complications of metabolic acidosis (4). To treat metabolic acidosis, patients are most often prescribed sodium bicarbonate, increasing sodium intake that could theoretically exacerbate comorbid conditions, such as hypertension and fluid overload. A higher intake of fruits and vegetables can have similar effects on serum bicarbonate levels (5).

In this issue of the *Clinical Journal of the American Society of Nephrology*, Bushinsky *et al.* (6) examined the effectiveness of a new potential therapeutic option, TRC101 (a sodium-free hydrochloric acid binding agent), in treating patients with CKD-associated metabolic acidosis. Because the compound is sodium free, it avoids possible complications associated with a sodium load. The investigators conducted a double-blinded, placebo-controlled, multicenter study in Eastern Europe (Bulgaria and Georgia); 135 patients with CKD (eGFR of 20 to <60 ml/min per 1.73 m^2) and serum bicarbonate levels of 12–20 mEq/L were enrolled and randomized to different treatment groups. The study period was 14 days, during which participants were hospitalized and received a controlled study diet and one of four doses of TRC101 (1.5 g twice daily, 3 g twice daily, 4.5 g twice daily, or 6 g once daily) or placebo (microcrystalline cellulose). After the treatment period, participants were discharged home and followed for 7–14 days off TRC101 to evaluate for adverse side effects and effects of treatment cessation. Patients given TRC101 had a significant rise in serum bicarbonate within the first 3 days of initial dose, and at completion of therapy, they had statistically significant elevations in serum bicarbonate compared with patients who received placebo (mean increase of 3.2–3.9 mEq/L; $P<0.001$). Using this drug, serum bicarbonate normalized in 35% of the treatment group, whereas levels in the placebo group did not change significantly. No notable changes in serum sodium, potassium, calcium, chloride, magnesium, or phosphate were observed during study period. After treatment termination, no significant safety events occurred, and serum bicarbonate levels declined back to near-baseline levels.

This study is the first to test this new medication, TRC101, which seems to be effective in increasing serum bicarbonate levels, but the study also raises several important questions. The first question pertains to the study population. The participants in the study had very low bicarbonate levels (mean =17.7 mEq/L; SD=1.2) for their level of eGFR (mean =35 ml/min per 1.73 m^2; SD =13) in the setting of normal serum phosphate levels (mean =3.7 mg/dl; SD=0.7). Population studies suggest that serum bicarbonate levels decrease starting at eGFR levels <30 ml/min per 1.73 m^2 (7). The population consisted of 70% patients with diabetes; therefore, some of the metabolic acidosis seen at a high eGFR may be due to type 4 renal tubular acidoses. Baseline serum potassium levels were not included in the tables. Additionally, the study was performed in the countries of Bulgaria and Georgia. There is no mention of race or ethnicity; thus, it is likely an all European sample, making findings less generalizable to the diverse United States and worldwide populations.

Significantly, this study excluded patients with New York Heart Association class 3 or 4 symptoms of heart failure and patients with systolic BP >170 mm Hg. Although edema was not an exclusion criterion, only 14% of their participants had clinical edema, and only 21% of the population had heart failure. Thus, the study population was a fairly healthy CKD population as appropriate for testing a new medication.

The study was conducted in an inpatient setting with participants eating a fixed diet. It is not clear what happens with this medication when taken under home conditions. The study setting was a regulated environment where many factors were controlled for, most importantly diet and medication administration. Patients received a diet designed to minimize dietary-based changes in serum bicarbonate levels. It would be noteworthy to see if similar increases in serum bicarbonate are seen with TRC101 treatment when the diet is under the patient's control. Additionally, TRC101 was not administered within 4 hours of other medications. This may present a logistic barrier to taking this medication in the real world, because patients with CKD are often on multiple other medications. TRC101 will need to be further studied for drug-drug interactions.

One notable result of the study was the increase in serum bicarbonate levels without an observed plateau over the 14 days of treatment on the study drug. Serum bicarbonate levels steadily increased throughout the

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study period, and although they returned to baseline on follow-up, it is unclear if the studied doses are the correct ones to treat acidosis without overcorrection. Because high serum bicarbonate levels are also associated with poor outcomes, notably heart failure (8), this medication will need to be very closely monitored to avoid overcorrection.

Mechanistically, TRC101 does not achieve increases in serum bicarbonate *via* exogenous bicarbonate delivery but rather, by selective binding of H^+ and Cl^- in the gut. The effects on the serum electrolytes over the course of the study are somewhat puzzling. Most alkali studies (sodium bicarbonate based) show a decrease in serum potassium levels, but there was no change in potassium levels in the patients on TRC101. Given the binding and removal of H^+ and Cl^- with the resulting increase in serum bicarbonate, it is unclear why Cl^- levels did not decrease with treatment. This suggests that the anion gap decreased, because there are no changes in any of the other components of the anion gap other than bicarbonate. Does this medication somehow change the gut microbiome by changing the gut pH and alter organic ion production and absorption in the gut? It is unclear and needs to be further studied.

Treatment with TRC101 appeared to quickly and effectively correct metabolic acidosis over 14 days in participants with CKD and was well tolerated with minimal reported side effects. An agent that can safely accomplish this without an increase in sodium load may serve as an alternative to currently used alkali medications. Notably, however, a diet rich in fruit and vegetables, an inexpensive intervention, has been shown to have similar effects to sodium bicarbonate therapy and may have similar effects to TRC101 as well (5). Importantly, despite small studies of sodium bicarbonate therapy showing benefits for clinical outcomes (9–11), a large, definitive study evaluating meaningful clinical outcomes, such as progression of kidney disease, has not yet been reported. Such a trial is needed to prove that treatment of metabolic acidosis improves patient outcomes.

In summary, TRC101 is a promising new medication to improve the metabolic acidosis associated with CKD. Future studies to more definitively conclude whether TRC101 is as or more beneficial than drugs currently in use would be studies including participants who have higher BP and glucose than in this study as well as more significant heart failure. These patients are excluded from most studies of sodium bicarbonate, but they are the patients at highest risk for disease progression. Further needed studies include studies testing TRC101 efficacy in a more ethnically diverse population, studies following participant-controlled daily routines and diets, and studies for a longer treatment duration to identify optimal dosing (alkalinization without overcorrection). Ultimately, because the goal is to show that TRC101 is equivalent, if not better, than current treatments, future studies could include a comparison of outcomes between patients treated with TRC101 and patients treated with currently used exogenous base therapy. Hopefully, the introduction of TRC101 will lead to continued interest in understanding how and why nephrologists should treat metabolic acidosis in CKD.

Disclosures

None.

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See related article, "Randomized, Controlled Trial of TRC101 to Increase Serum Bicarbonate in Patients with CKD," on pages 26–35.