Chronic Selective Endothelin A Receptor Antagonism Reduces Serum Uric Acid in Hypertensive Chronic Kidney Disease

To the Editor:

Epidemiological studies report a relationship between serum uric acid concentrations (sUA) and a wide variety of cardiovascular conditions, including hypertension, metabolic syndrome, diabetes, coronary artery disease, cerebrovascular disease, pre-eclampsia, and chronic kidney disease (CKD).

Indeed, sUA is considered by some to be an independent risk factor for both cardiovascular disease and CKD. Others have noted that an elevated sUA predicts the development of hypertension, obesity, diabetes, and CKD. Importantly, emerging clinical data show that lowering sUA has both cardiovascular and renal benefits.

Endothelin (ET) 1 is the most potent endogenous vasoconstrictor produced within the vasculature. It is implicated in both the development and progression of CKD. Its effects are mediated via 2 receptors, the ET-A (ET\(_A\)) and ET-B (ET\(_B\)) receptors, with the major pathological effects being ET\(_A\) receptor mediated. We have shown recently that chronic selective ET\(_A\) receptor antagonism reduces proteinuria, blood pressure, and arterial stiffness in patients with nondiabetic, hypertensive, proteinuric CKD, effects that are potentially renoprotective. The current data show the effects of sitaxsentan and placebo on sUA in this same cohort of CKD patients.

The rationale and design for this study have been reported in detail elsewhere. In brief, a randomized, double-blind, 3-way crossover study, 27 subjects on recommended renoprotective treatment received 6 weeks of placebo, sitaxsentan 100 mg once daily and nifedipine LA 30 mg once daily. Twenty-four-hour proteinuria, urine protein:creatinine ratio, 24-hour ambulatory blood pressure, and pulse wave velocity, as an index of arterial stiffness, were measured at baseline, week 3, and week 6 of each treatment period. sUA was also assessed at these same time points.

Baseline sUAs were raised into the frankly hyperuricemic range in both placebo and sitaxsentan phases of the study, with placebo at 476 ± 20 μmol/L and sitaxsentan at 506 ± 21 μmol/L. Baseline sUA was inversely related to baseline proteinuria (r² = 0.19; P = 0.02). Although placebo had no effect on sUA, sitaxsentan reduced sUA by ~11% by study end. This effect was as apparent at week 3 as at week 6 of the study phase (Figure). The reduction in sUA was not associated with changes in blood pressure, renal blood flow, pulse wave velocity, or proteinuria.

Lowering sUA may reduce cardiovascular risk and CKD progression. In patients with mild renal disease (CKD stage 3), treatment of asymptomatic hyperuricemia led to delayed progression. Similarly, Kanbay et al showed an improvement in renal function after treatment of asymptomatic hyperuricemia.

Finally, in a different approach, Talaat and el-Sheikh withdrew the xanthine oxidase inhibitor allopurinol from a group of patients with stable CKD and found both worsening of hypertension and acceleration of renal dysfunction but only in those patients not taking an angiotensin-converting enzyme inhibitor. However, these studies suggesting benefits of reducing sUA all use allopurinol as their therapeutic agent. ET receptor antagonism offers a potentially novel approach to lowering sUA in patients with hypertensive CKD.

There are only 2 studies showing that ET receptor antagonism reduces sUA. Raichlin et al showed that 6 months treatment with the selective ET\(_A\) receptor antagonist atrasentan reduced sUA from 293 to 286 μmol/L in patients with early atherosclerosis. Change in sUA was not a primary end point in this study. In another small open-label study (n = 15) in patients with pulmonary arterial hypertension and no control group, Ulrich et al showed that 6 months of treatment with the mixed ET\(_{A/B}\) receptor antagonist bosentan lowered sUA from 353 to 305 μmol/L. The current data build on these studies by showing that, in patients with hypertensive CKD, selective ET\(_A\) receptor antagonism lowers sUA, which may contribute to both cardiovascular and renoprotection.

The mechanism for this potentially beneficial effect of ET\(_A\) receptor antagonism remains unclear. Removal of circulating sUA depends on the gut (1/3 excretion) and kidneys (2/3 excretion). Thus, blocking the effects of ET-1, at least at the ET\(_A\) receptor, may augment one or both of these. Nearly all sUA is filtered through the glomerulus since ~5% circulates without bound to serum proteins. Most of this is reabsorbed in the proximal tubule so that ~90% of filtered uric acid is reabsorbed. Since in the current study glomerular filtration rate fell, it is more likely that ET\(_A\) receptor blockade inhibits tubular reabsorption of filtered urate than increases its filtration. In addition, ET receptor antagonism may lower sUA through an antioxidant effect inhibiting its production. Larger studies are needed to confirm this important finding and define its mechanism, in a group of patients at very high cardiovascular risk.

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