Secretory Clearance Mediated by Organic Cation Transporter 2 Reduced in Parallel with Glomerular Filtration Rate in Patients with Chronic Kidney Disease Despite the Potential OCT2 Inhibition Effect by Uremic Solutes

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Purpose

More than 30% of top prescribed drugs in the U.S. are predominantly eliminated by the kidney whose pharmacokinetics (PK) are known to be affected by the impaired renal function. As the prevalence of chronic kidney disease (CKD) is increasing, it is important to know how the secretory clearance of a drug changes in deteriorating kidneys. Some evidences suggest that uremic solutes, which accumulate at high concentrations in CKD patients, might inhibit one of renal transporters in the kidney, Organic Cation Transporter 2 (OCT2). The goals of this study are to 1) review published papers to obtain information on changes of the secretory clearance of OCT2 substrate drugs in CKD patients, 2) perform a comprehensive in vitro inhibition screening on OCT2 with uremic solutes, and 3) evaluate the clinical relevance of uremic solutes on OCT2 inhibition.

Methods

OCT2 substrate drugs that are predominantly renally eliminated (fe ≥ 0.3) were identified from the University of Washington Metabolism and Transport Drug Interaction Database (UW DIDB). Clinical studies and new drug applications (NDAs) reporting PK in CKD patients were reviewed. Secretory clearance (CLsec) was calculated by subtracting filtration clearance from total renal clearance. The ratio of CLsec to the corresponding glomerular filtration rate (GFR) was calculated and compared for both healthy subjects and CKD patients with different stages of impaired renal function.

A total of 72 uremic solutes were evaluated to determine the potential interaction between uremic solutes and OCT2. The inhibition potencies of uremic solutes on OCT2 were accessed at 100 times the highest serum concentrations reported in CKD patients using metformin as the substrate. An inhibitor was defined as reducing the transport of metformin by more than 50% of the control. Values of IC50 were acquired and compared with highest clinical achievable concentrations of uremic solutes that are inhibitors.

Results

We reviewed 52 clinical papers and 8 NDAs reporting PK in CKD patients for 31 drugs transported by OCT2. Dexpramipexole, lamivudine, metformin, pilscainide, sepantronium bromide, and tiotropium were identified as OCT2 substrates that are mainly renally eliminated and have PK data in CKD patients. Secretory clearance of these drugs deteriorates approximately in parallel to GFR in CKD patients (see Figure). In vitro inhibition screening with uremic solutes showed that 7 out of 72 uremic solutes inhibited OCT2, which included creatinine, dimethylamine, oxidized glutathione, homocysteine, indoxyl-β-D-glucuronide, malondialdehyde, and trimethylamine. Although those uremic solutes might inhibit OCT2 at very high concentrations, the values of IC50 were all higher than the reported highest concentrations ([I]) in CKD patients ([I]/IC50 ranged from 0.02 for oxidized glutathione to 0.39 for dimethylamine).

Conclusion

Uremic solutes are less likely to be clinically relevant OCT2 inhibitors despite the fact that they accumulate to high concentrations in CKD patients. This is in agreement with our finding in this study that secretory clearance of six drugs potentially mediated by OCT2 declined approximately in parallel with GFR in CKD patients.