Effects of Renal Impairment on Transporter-Mediated Renal Reabsorption of Drugs and Renal DDI: A Simulation-Based Study
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Purpose
Renal clearance (CLR) is an important pathway of elimination for drugs with poor metabolism and biliary clearance. The objectives of this study were to evaluate the effects of renal impairment (RI) on: (1) pharmacokinetics (PK) of a drug that undergoes renal transporter-mediated active reabsorption, (2) transporter-mediated renal drug-drug interactions (DDI) when the transporter expression is altered, (3) PK of a probe drug with a wide range of protein binding, when the transporter expression is altered, and (4) active renal reabsorption of a drug whose metabolism is altered, with a focus on changes in its renal clearance.

Methods
We utilized a previously published semi-mechanistic kidney model incorporating physiologically-relevant fluid reabsorption and transporter-mediated active renal reabsorption (PMID: 26341876) in this study. The probe drug/transporter pair utilized was [gamma]-hydroxybutyric acid (GHB) and monocarboxylate transporter 1 (SCL16A1, MCT1). GHB concentrations in the blood and amount excreted into urine were simulated for the IV dose range of 200-1500 mg/kg in rats using the model. Renal impairment was incorporated into the model by including glomerular filtration rate (GFR) as a parameter and perturbing its value from 2.2 mL/min (100% renal function) to 0.22 mL/min (10% renal function). To study MCT1-mediated DDI, non-competitive inhibition of MCT1 was included in the model. Transporter capacity parameter (VMAX) was modified using the parameter [I]/KI, or R, which was varied from 0 to 100, where 0 is the absence of transporter inhibition. Perturbations in the expression of MCT1 and drug metabolizing enzymes (DMEs) were incorporated into the model by increasing or decreasing the value of VMAX of GHB transport across the basolateral and brush-border membranes of proximal tubules cells in kidneys and VMAX, of GHB metabolism, respectively. All simulations were performed using SIM module in ADAPT5. AUC0,inf were obtained using the NCA feature in PKSolver add-on package in MS Excel. CLR was calculated as the ratio of amount of GHB excreted unchanged into urine at time infinity (Ae,inf) and AUC0,inf.

Results
A decrease in renal function (GFR) resulted in an increase in GHB concentrations in blood as a consequence of a decrease in its CLR. CLR decreased by >100-fold when the renal function decreased to 10% for all doses. Although renal impairment decreased Ae,inf for all doses of GHB, the time to achieve Ae,inf was unchanged. For all perturbations in transporter expression and renal function, the maximal CLR was achieved when R was 100 and CLR approached GFR. When R was 100, CLR was dependent on the renal function. Decreases in fraction unbound (fu) or GFR resulted in lower values of CLR. Decrease in CLR was observed when values of both GFR and fu were also decreased (10% GFR and fu = 0.1). In this case, CLR decreased from 1.03 mL/min to 4.05 x 10^-5 mL/min: a decrease of over 25,000-fold. Similar reduction in CLR was observed when either fraction unbound or renal function was decreased by a specific percentage for all perturbations in transporter expression. Increased DME expression resulted in (1) lower GHB concentrations in the blood, (2) reduced time to achieve Ae,inf, and (3) very slight increase in CLR the converse held true when DME expression was decreased. The effect of renal impairment was reduced when DME expression was increased as a result of increased metabolic and overall clearances, causing CLR to be a smaller percentage of overall clearance.

Conclusion
This study demonstrated that renal function is a major determinant in the clearance of drugs undergoing transporter-mediated renal reabsorption. The effect of renal function on the clearance of drugs is modulated by transporter expression, contribution of renal clearance to overall clearance, expression of DMEs, fraction unbound, and drug-drug interactions with inhibitors of renal transporters. These findings highlight the importance of understanding the role of renal function-dependent drug-drug and drug-transporter interactions in the renal clearance of compounds.

Support: NIH grant R01DA-023223