A Meta-Analysis of the Pharmacokinetics of Hepatically-Cleared Drugs in Patients with Renal Impairment
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Purpose
Chronic kidney disease (CKD) can affect the pharmacokinetics (PK) of hepatically-cleared drugs, causing increased exposure in patients with renal failure. Therefore, the FDA recommends that sponsors conduct clinical studies for highly metabolized drugs and assess whether a dose should be adjusted in renal patients. To elucidate mechanism for the cases that increased exposure in CKD patients versus those that did not, we conducted a thorough meta-analysis of published PK literature for hepatically-cleared drugs and examined PK alteration.

Methods
We searched PubMed for human PK studies in both normal and kidney disease subjects and collected data for 52 highly metabolized drugs, excluding drugs that were primarily eliminated by the kidney. We grouped the drugs as either “PK-altered” or “PK-unaltered”, and analyzed the statistical tests performed. We also analyzed whether the drugs were substrates, inhibitors, and inducers to transporters and/or metabolizing enzymes.

Results
Among 52 drugs, 22 were classified as “PK-altered”, consistent with kidney failure affecting metabolism, transporters or both. Of the remaining 30 drugs classified as “PK-unaltered”, 27% were from studies that were either underpowered or misrepresented (no patients with severe impairment, GFR<30ml/min), therefore, may lack the proper scientific basis for concluding an insignificant CKD effect. While most of the 52 drugs were substrates to one or more CYP enzymes, we also found that 96% of the “PK-unaltered” substrates were also inhibitors or inducers of their major enzymes (40% for PK-altered), which may increase variability and mask any PK alterations in CKD. For telithromycin and nefazodone, PK changed significantly in multiple dosing but not in single administration. For nicardipine, PK changed significantly in severe renal impairment but not in patients with regular hemodialysis treatment.

Conclusion
The distinctions between “PK-altered” vs. “PK-unaltered” drugs studied in CKD patients were unclear because 1) mixed effect of the substrate vs. inhibitor/inducer of metabolism, 2) patient population differences and misrepresentation, and 3) large inter-subject variability. Since these factors may impact the conclusion drawn from the renal impairment studies and labeling, proper study design for testing drugs in CKD patients should be considered.