Effect of Liver Disease-Mediated Alterations in Hepatic Transporter Function on the Pharmacokinetics and Hepatobiliary Disposition of Drugs

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Purpose
Liver disease can alter hepatic transporter function and markedly impact drug and bile acid (BA) disposition. These changes may have important implications for optimizing pharmacotherapy. Understanding the impact of such changes on drug pharmacokinetics (PK) and hepatobiliary disposition of transporter substrates can improve our ability to assess and predict hepatic transporter-mediated drug interactions and drug-induced liver injury (DILI) in specific patient populations. These studies were designed to elucidate the effects of a progressive inflammatory form of liver disease, non-alcoholic steatohepatitis (NASH), and autosomal dominant polycystic kidney disease (ADPKD) [a disease also affecting the liver that has been associated with tolvaptan-mediated DILI] on hepatic transporter function, drug/substrate disposition, and BA homeostasis using clinical, preclinical and in vitro studies.

Methods
The effect of NASH on hepatic transporter function and drug/substrate disposition was evaluated in patients (n=4/cohort) using the hepatobiliary imaging probe $^{99m}$Tc-mebrofenin (MEB). Liver scintigraphy and blood concentration-time profiles were obtained after a 2.5mCi i.v. dose. To elucidate the mechanistic basis for tolvaptan-mediated alterations in hepatic transporter function, in vitro studies with human hepatic BA transporter expression systems for NTCP, BSEP, MRP2, MRP3, and MRP4 were conducted to determine the inhibitory effect (i.e., IC$_{50}$) of tolvaptan and two major metabolites, DM-4103 and DM-4107, on transporter function (n=3 independent experiments). Additionally, the hepatobiliary disposition of endogenous BAs and carboxydichlorofluorescein (CDF), a substrate of the hepatic transporters Oatp, Mrp2 and Mrp3, was assessed in polycystic kidney (PCK) rats, a rodent model of ADPKD. BAs in the liver and serum of PCK and wild-type rats were quantified by LC-MS/MS (n=4 rats/cohort). Hepatic cyst volume in PCK rats was measured using magnetic resonance imaging. Livers from PCK and wild-type rats were perfused ex vivo with CDF in a single-pass manner (n=5 rats/cohort). Mrp2 and Mrp3 proteins were visualized in rat liver tissues using immunohistochemical techniques.

Results
NASH significantly increased MEB systemic and hepatic exposure (AUC$_{0-\infty}$) by 1.5- and 7-fold, respectively; maximal blood concentration (C$_{max}$) and liver activity (X$_{max}$) were increased by 2.2- and 4.4-fold, respectively. MEB blood clearance (CL$_{blood}$) was decreased to 5.4 mL/min/kg in NASH from 16.4 mL/min/kg in healthy volunteers. Tolvaptan, DM-4103, and DM-4107 inhibited key human hepatic BA transporters, as evidenced by IC$_{50}$ values. DM-4103 exhibited a C$_{max}$/IC$_{50}$ value $>$0.1 for NTCP, BSEP, MRP2, MRP3, and MRP4. Mean total BAs and toxic BAs (TDCA, TCDCA, GDCA, and GCDCA) were significantly increased by 13.2- and 8.4-fold, respectively, in the liver of PCK rats. Hepatic GCDCA concentrations were increased 22.8-fold relative to wild-type rats. Total serum BAs were significantly increased by 5.5-fold in PCK rats, and positively correlated with markers of liver impairment such as liver weight (p<0.01), total liver BAs (p<0.01), total toxic liver BAs (p<0.001), and cystic volume (p<0.001). The biliary clearance (CL$_{biliary}$) of CDF was significantly reduced by ~300-fold in PCK rats (1.22 mL/min in wild-type versus 0.00375 mL/min in PCK rats). Protein expression of Mrp3, but not Mrp2, was increased in PCK rats.

Conclusion
This is the first clinical data to describe NASH-associated functional alterations in hepatic drug disposition. The systemic and hepatic exposure of drugs such as MEB that are OATP/MRP2/MRP3 substrates may be significantly altered in NASH patients. Novel in vitro and preclinical data demonstrate the inhibition of BA transporters by tolvaptan and metabolites, and altered hepatobiliary disposition of Oatp/Mrp2/Mrp3 substrates and endogenous BAs in PCK rats. These data suggest that ADPKD patients may be more susceptible to hepatic transporter-mediated drug interactions and DILI due to altered hepatic transporter function and hepatocyte accumulation of toxic BAs. This dissertation research highlights the importance of understanding the consequences of liver disease-mediated alterations in hepatic transporter function in order to optimize pharmacotherapy and minimize toxicity.

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