Introduction:

MMP2 (ABCC2): Efflux transporter mediating the biliary excretion of many drugs from hepatocytes. Deficiency in its transport capacity → Toxic accumulation of drugs in the liver and drug-induced liver injury.

Need for quantitative imaging techniques to explore MMP2 activity but the presence of other transporter systems in hepatocytes and the liver metabolism complicate the interpretation of kinetic imaging data.

Materials and Methods:

MMP2 inhibitors tested: rifampicin (RIF), diltiazem (DTZ) and ciclosporin A (CsA) [2]

Control

RIF 40 mg/kg IV

DTZ 20 mg/kg SC

CSA 0.5 mg/kg IV

Results:

Pharmacokinetic modeling of MEB:

Significant and comparable decrease in $k_5$, suggesting effective MMP2 inhibition with all inhibitors compared to control.

RIF and the highest doses of DTZ and CSA significantly decreased $k_5$ compared to control. The effect was dose-dependent with no impact of the lowest dose of DTZ and CSA.

Doppler Ultrasound to assess liver perfusion (portal vein, hepatic vein and hepatic artery respectively):

High doses of DTZ but not of CSA decreased the hepatic blood flow in the portal vein and hepatic artery.

Discussion:

RIF is a potent and non-selective MMP2/OATP inhibitor used for drug-drug interaction studies while CsA and DTZ are known to extensively inhibit MMP2 in vitro with no or little effect on OATP [3, 4]. Our results confirm that CSA and DTZ are potent inhibitors of the canalicular MMP2-mediated efflux of MEB in vivo. The lowest doses of DTZ and CSA had no impact on the sinusoidal influx ($k_1$) while effectively inhibiting the biliary excretion ($k_5$). This suggests that DTZ and CSA are more potent at inhibiting canalicular MMP2 than OATP in vivo. In addition, low dose CsA can be safely administered to humans and is not likely to impact liver perfusion.

Reference: