Determination of the MRP2-mediated transport capacity at the liver - bile interface using an improved ^{99m}Tc-mebrofenin imaging protocol

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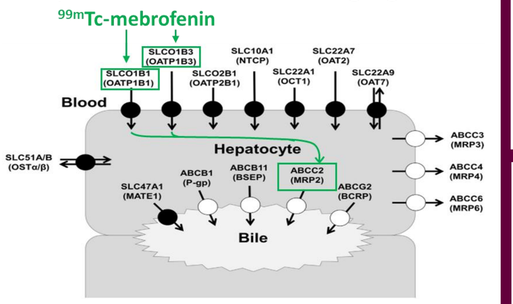
Introduction :

MRP2 (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 MRP2 activity but the presence of other transporter systems in hepatocytes and the liver metabolism complicate the interpretation of kinetic imaging data.



^{99m}Tc-mebrofenin (MEB) : Metabolically stable probe for hepatic scintigraphy imaging selectively transported by MRP2 on the canalicular interface, but its liver kinetics are also highly dependent on the uptake transporters OATP (SLCO) [1] .

Objective :

Develop and validate a pharmacological protocol to selectively inhibit the MRP2-mediated canalicular transport of MEB without impacting the OATP-mediated influx, thus providing a substrate/inhibitor pair to selectively reveal the transport capacity of MRP2 *in vivo*.

Materials and Methods :

MRP2 inhibitors tested : rifampicin (RIF), diltiazem (DTZ) and ciclosporin A (CsA) [2]

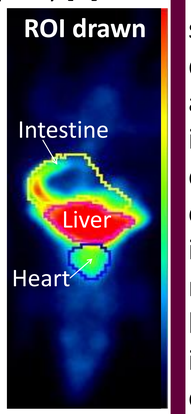
n = 5-6 in each condition

- Control
- RIF 40 mg/kg IV
- DTZ 10 mg/kg SC
- DTZ 20 mg/kg SC
- DTZ 40 mg/kg SC
- CsA 0,01 mg/kg IV
- CsA 0,1 mg/kg IV
- CsA 0,5 mg/kg IV
- CsA 1 mg/kg IV
- CsA 5 mg/kg IV

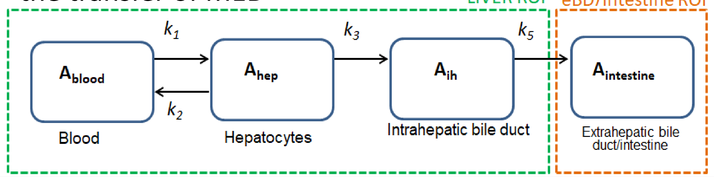
^{99m}Tc-mebrofenin
(39 ± 4 MBq IV)

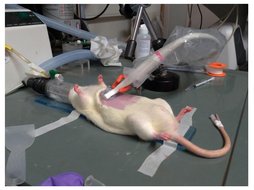
^{99m}Tc

Planar dynamic scintigraphy acquisition (40 min)



Pharmacokinetic modeling to describe the transfer of MEB





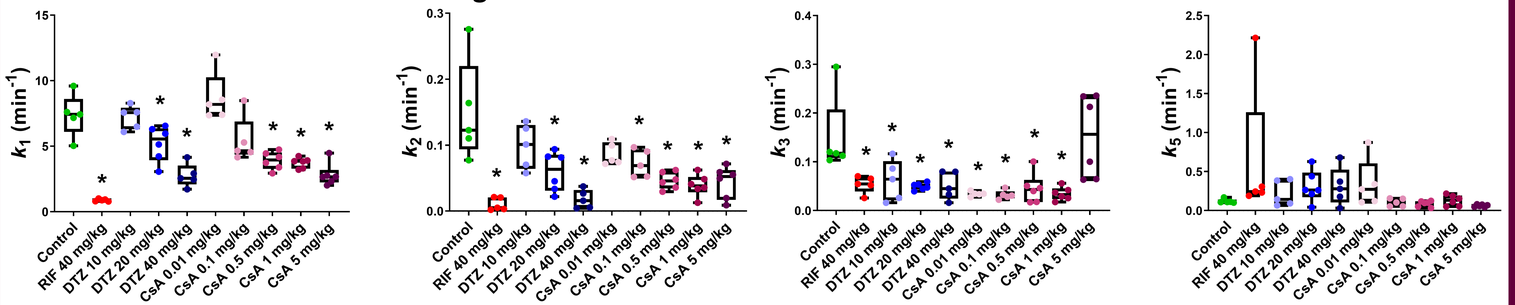
Doppler Ultrasounds to assess the liver perfusion before and after injection of:

- RIF 40 mg/kg IV
- DTZ 3 mg/kg IV
- CsA 5 mg/kg IV

n = 4 in each condition

Outcome parameters were compared using one-way ANOVA for imaging data and a paired t-test for ultrasound results.

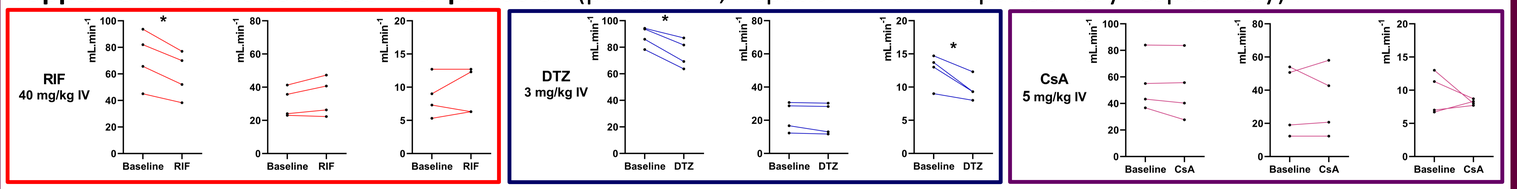
Results : Pharmacokinetic modeling of MEB :



→ Significant and comparable decrease in k_3 suggesting effective MRP2 inhibition with all inhibitors compared to control.

→ RIF and the highest doses of DTZ and CsA significantly decreased k_1 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 MRP2/OATP inhibitor used for drug-drug interaction studies while CsA and DTZ are known to extensively inhibit MRP2 *in vitro* with no or little effect on OATP [3, 4]. Our results confirm that CsA and DTZ are potent inhibitors of the canalicular MRP2-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_3). This suggests that DTZ and CsA are more potent at inhibiting canalicular MRP2 than OATP *in vivo*. In addition, low dose CsA can be safely administered to humans and is not likely to impact liver perfusion.

Conclusion :

Low dose CsA selectively inhibits the MRP2-mediated excretion of MEB at the liver-bile interface. MEB without/with CsA (0.01 mg/kg) therefore provides a clinically feasible substrate/inhibitor combination to selectively quantify the hepatic MRP2 transport capacity *in vivo*.

References :

[1] Neyt, 2013, J. Nucl. Med.
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[4] Matsson, 2009, Pharm Res.

No disclosure

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