EX VIVO WHOLE LIVER PERFUSION MODEL FOR PREDICTION OF DRUG-DRUG INTERACTIONS AND BILIARY EXCRETION OF ROSUVASTATIN

Introduction
Current models to predict biliary excretion often fail due to species differences (rodent/dog) or due to differences in transporter expression in in vitro assays (e.g., sandwich cultured hepatocytes). Especially when drugs are subjective to enterohepatic circulation (EHC), this results difficulties to predict plasma profiles after oral and iv administration. Moreover, in case a compound is subjective to EHC, it is more prone to cause any drug-drug interaction and/or drug induced liver injury.

Goal
In order to study the feasibility to set-up a preclinical model to investigate hepatic clearance, biliary excretion and the effect of drug-drug interaction on these processes, we have applied whole porcine liver on a pressure-controlled perfusion machine (LiverAssist).

Approach
Prior to isolation of the liver from the anaesthetized pigs, the blood was heparinized, portal vein and hepatic artery were cannulated and directly after cutting the hepatic inferior vena cava the liver was flushed with warm Ringers buffer. Bile duct was cannulated directly after positioning of the liver on the Liver Assist device, on which it underwent normothermic perfusion at 37°C. Rosuvastatin (3 mg bolus injection) was used to model compound to study hepatic clearance and biliary excretion in the absence and presence of rifampicin (600 mg/h, continuous infusion). Blood samples were taken 15, 30, 45 and 60 minutes after dosing and bile was collected in 15 min fractions.

Results
First steps in development of this ex vivo perfused porcine liver model:
- Demonstrator study showing feasibility of the application of ex vivo perfused porcine liver as good model to study hepatic clearance and biliary excretion of drugs
- In the presence of rifampicin, biliary excretion of rosuvastatin was decreased to 20% of the dose (whereas 100% when rosuvastatin was dosed alone), and plasma AUC was 200-fold increased

Conclusions / next steps:
- We have successfully developed an ex vivo liver perfusion model to study hepatic clearance and biliary excretion of drugs and the effect of drug-drug interaction on these processes.
- Next studies will be focused on studying hepatic metabolism, the effect of long-term liver perfusion on hepatic transporter expression and the possibility to apply diseased human livers which become redundant after liver transplantation.
- For these projects TNO is looking for partners to further co-develop these models.

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