A5. Normothermic Machine Perfusion of Diseased Explanted Livers to Study Hepatic Pharmacokinetic Processes

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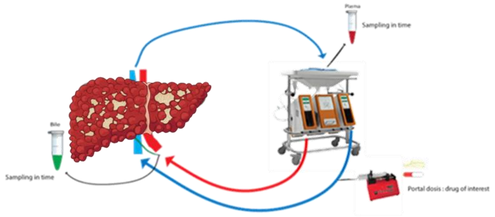
Introduction

The prediction of hepatic clearance and biliary excretion is of high importance to assess the pharmacokinetics of drugs. This is particularly important in patients with hepatic diseases where altered liver function can result in an altered pharmacokinetic profile of the administered drugs

The aim of this study was to develop a physiologically relevant human pre-clinical liver disease model to investigate (differences in) drug pharmacokinetics utilizing normothermic machine perfusion (NMP) of explanted livers of patients undergoing liver transplantation

METHODS



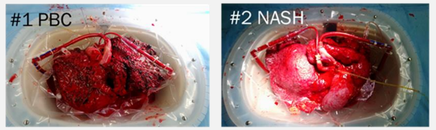
1. Inclusion of patients with end-stage liver disease undergoing liver transplantation
2. Removal of diseased liver during surgery
3. Immediate flush of portal vein and hepatic artery
4. Reconstruction and cannulation of portal vein, hepatic artery and bile duct
5. Initiation of pressure controlled machine perfusion at 37°C
6. Hourly blood gas analysis to study liver viability
7. After 120 min of perfusion, a cocktail of model drug compounds (Rosuvastatin, metformin and furosemide) was administered to study drug clearance
8. Plasma and bile and tissue samples were taken at prespecified times

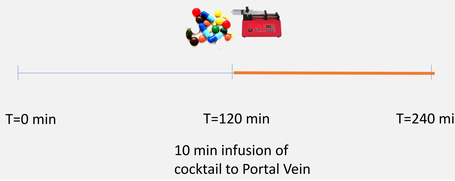
Inclusions

Table 1. Inclusion of different liver diseases, cirrhotic vs non-cirrhotic

	Liver disease	Disease severity score
Cirrhotic livers (n=6)	#1 PBC	23
	#2 NASH	19
	#3 ALD	14
	#5 ALD + HCC	9
	#7 ALD	10
	#8 NASH	11
Non-cirrhotic Livers (n=3)	#4 HBV + HCC	6
	#6 Research liver	X
	#9 Research liver	X

PBC: Primary Biliary Cholangitis, **NASH**: Non Alcoholic Steato-Hepatitis, **ALD**: Alcoholic Liver Disease **HCC:** Hepatocellular Carcinoma **HBV**: Hepatitis B Virus, **Research Liver:** marginal liver (declined for transplantation)





Results

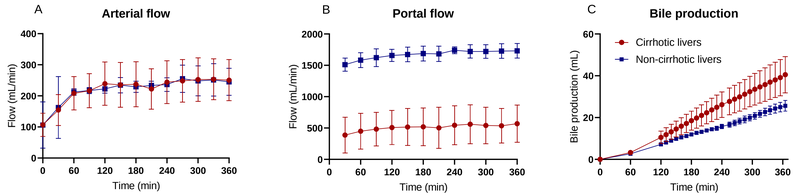


Figure 1. Flow and bile production during ex vivo porcine liver perfusion. (A) Portal flow (B) Arterial flow and (C) total bile production during 360 min of perfusion Data represents mean ±SD

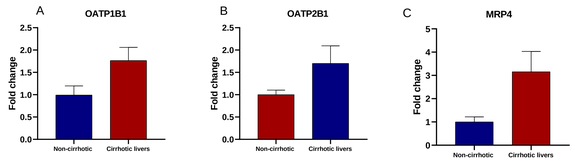
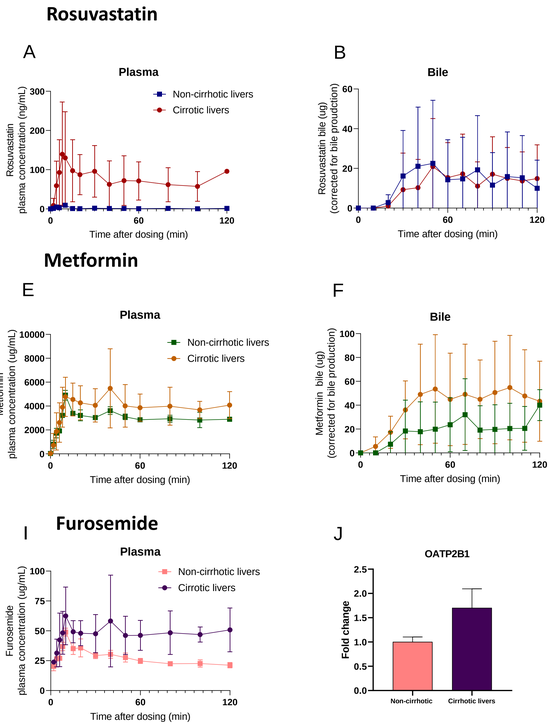


Figure 2. (A) OATP1B1 (B) OATP2B1 (C) MRP4 expression in cirrhotic and non-cirrhotic livers measured in biopsies from t=0 (non cirrhotic n=3, cirrhotic n=6). Data represents fold change ±SD



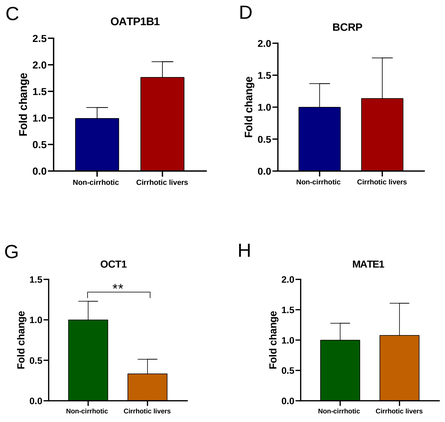


Figure 3. Pharmacokinetic en transporter gene expression data ex vivo diseased livers.

Rosuvastatin clearance in (A) Plasma concentration and (B) bile (C) OATP1B1 expression and (D) BCRP expression at t=0 min.

Metformin clearance shown in (E) plasma and (F) Bile samples, (G) OCT1 and (H) MATE1 expression at t=0 min of perfusion.

Furosemide clearance shown in (I) plasma and (J) OATP2B1 expression at t=0 min of perfusion

(Data represents mean ±SD, non cirrhotic n=3, cirrhotic n=6)

Conclusions

Able to perfuse diseased explanted ex vivo liver to study drug pharmacokinetics during ex vivo liver perfusion

- Show differences in plasma uptake and biliary excretion between cirrhotic and non-cirrhotic livers
- Differences in transporter expression in cirrhotic and non-cirrhotic livers
- Getting more insight into functioning of the liver in drug clearance and excretion

Future Research

- Porcine and human kidney perfusion to study renal clearance
- Combined porcine liver + kidney perfusion to study % renal and % biliary clearance