PREDICTING HUMAN PHARMACOKINETICS BY USING EX VIVO MODELS AND PBPK MODELING; DEMONSTRATOR STUDY USING ROSUVASTATIN AND DIGOXIN

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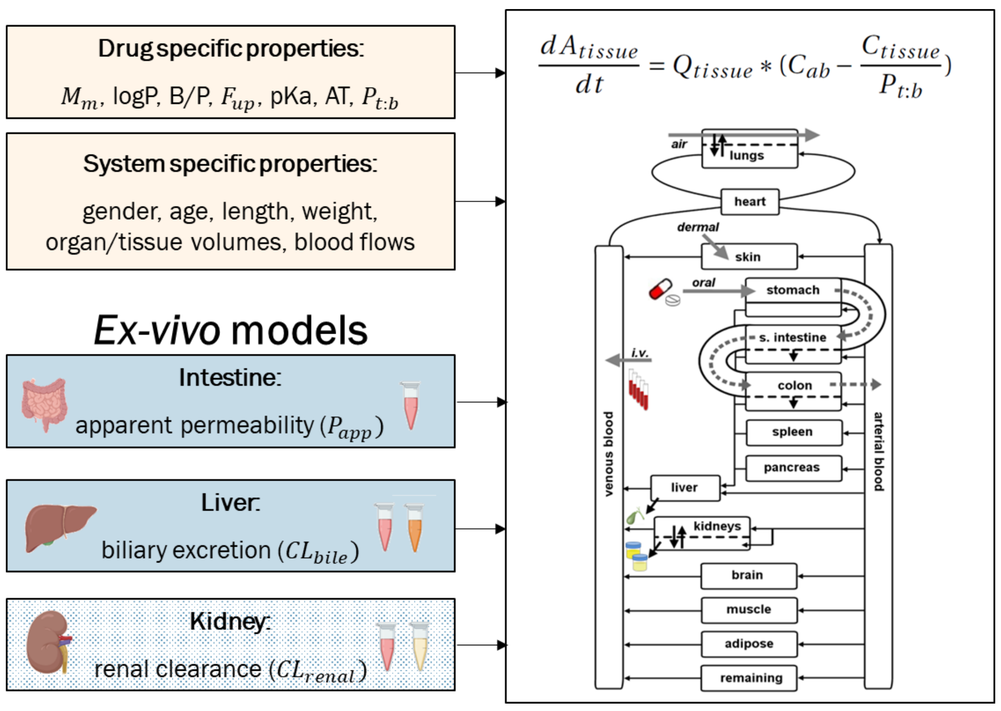
INTRODUCTION

The prediction of hepatic clearance and biliary excretion is of high importance to assess the pharmacokinetics of drugs. Ex vivo whole organ models, are a promising tool compared to in vitro models, thereby paving the way to apply physiologically-based pharmacokinetic (PBPK) modeling in a more reliable and accurate way.

AIM

To demonstrate and incorporate ADME data of 2 model drugs (rosuvastatin and digoxin) derived from intestinal segment studies and whole organ perfused liver and kidney into a generic PBPK model to predict the drug PK profile in humans.

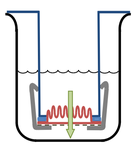
METHODS



Two *ex vivo* models were developed using porcine organs to study ADME processes of rosuvastatin and digoxin. The generated data was subsequently incorporated in a generic PBPK model:

1) Intestinal regional transport

Intestinal transport of rosuvastatin and digoxin was determined using the InTESTine system



- Porcine jejunum, ileum & colon tissue
- Assessment of apical to basolateral transport

2) Liver & kidney perfusion

Combined liver kidney perfusion was performed to study biliary end renal clearance

- Cannulation liver: hepatic artery & portal vein
- Cannulation kidney: renal artery
- Slow bolus dosing via portal vein
- Perfusate, bile and urine samples taken in time

3) PBPK modelling

A generic PBPK model was subsequently developed with the input of drug specific properties and system specific properties

Ex vivo models input:

- InTESTine: regional Papp data
- Liver & kidney perfusion derived data

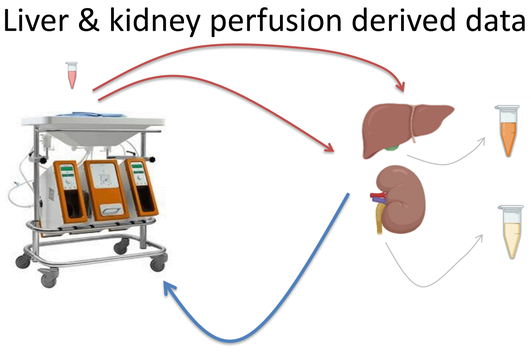
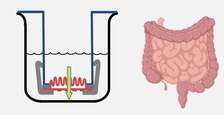


***Figure** 1. Graphical representation of combined ex vivo liver and kidney perfusion; generating perfusate, bile and urine fractions.*

RESULTS

1) Intestinal regional transport



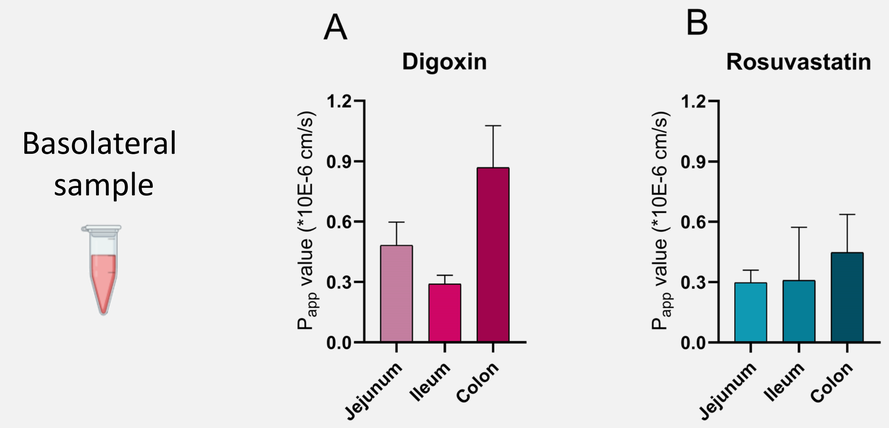


***Figure 2.** Papp values in jejunum, ileum and colon of (A) Digoxin and (B) rosuvastatin. Data represents mean ±SD (n=3)*

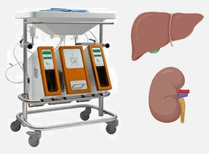
Digoxin:

- limited absorption (average Papp 0.57, due to PgP affinity)
- Showing higher Papp values in de distal parts of GI tract (P_{app} 0.87)

Rosuvastatin:

- Similar results were found for rosuvastatin (BCRP substrate), with average P_{app} value of 0.29 and 0.31 for jejunum and ileum and 0.4 for distal GI tract

2) Hepatic, biliary and renal clearance



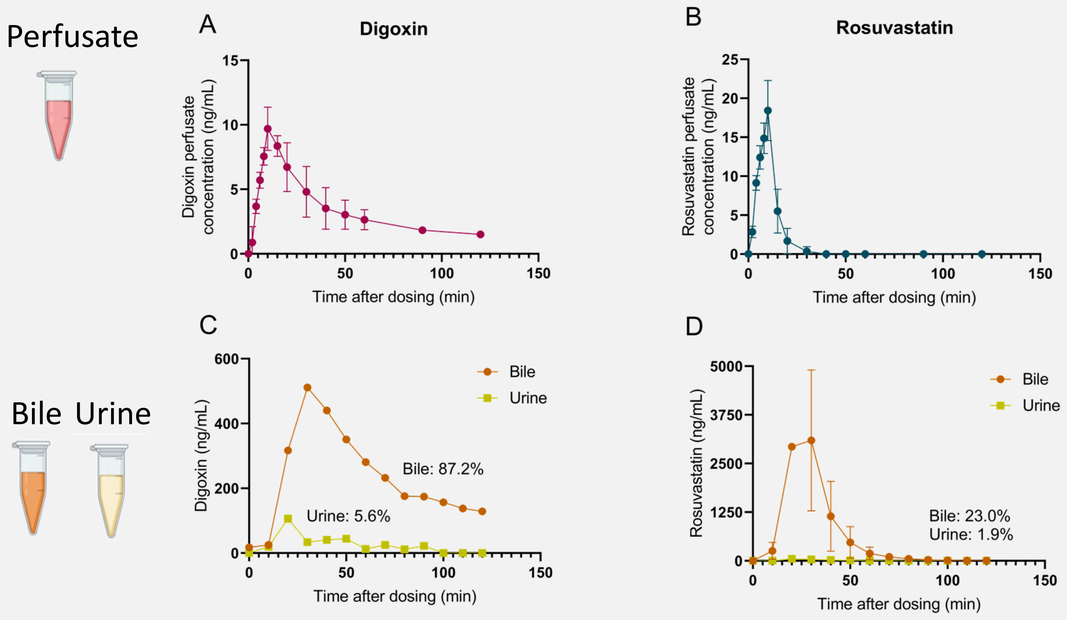
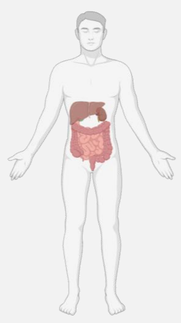


***Figure 3**. Pharmacokinetic profiles of ex vivo liver and kidney perfusion model (A) Perfusate clearance of digoxin and (B) rosuvastatin. Biliary and urinary fractions were measured for (C) digoxin and (D) rosuvastatin. Data represents mean ±SD (n=1/n=2)*

- Major route of elimination via bile for both compounds
- Minor urinary excretion

3) PBPK modelling



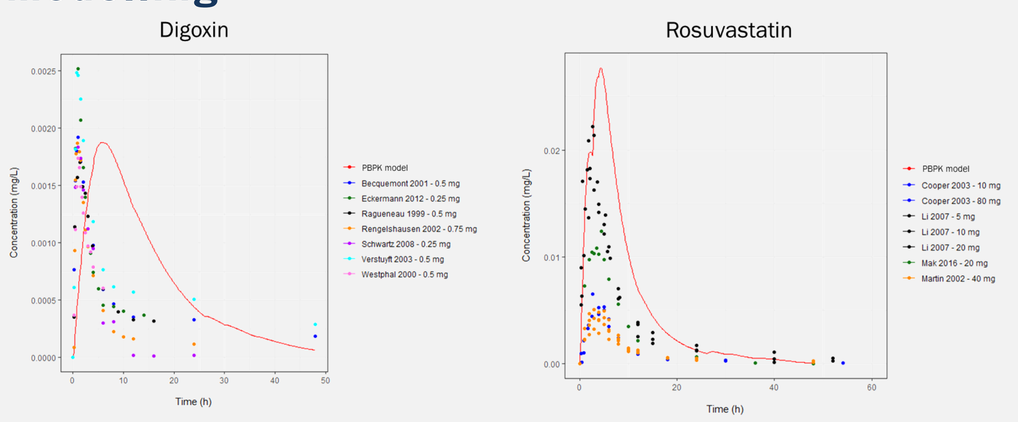


***Figure 4.** Simulated plasma profile of (A) digoxin and (B) rosuvastatin compared to clinical data*

Table 2. The simulated and clinical values for bioavailability, renal and fecal excretion for digoxin and rosuvastatin

Drug		Bioavailability	Renal	Fecal
Digoxin	Simulated	72%	64%	36%
	Clinical	70-80%	primary	-
Rosuvastatin	Simulated	Absolute: 45% Relative: 47%	44%	56%
	Clinical	Absolute: 20% Relative: 50%	10%	90%

***Table 3.** The simulated vs. clinical pharmacokinetic parameters for single PO dose of 0.5 mg digoxin or 10 mg rosuvastatin*

	Parameter	Simulated	Clinical data
Digoxin	C_{max} *(ng/mL)*	1.90	2.50 ± 0.70
	T_{max} *(h)*	5.80	1.50 (0.8-2.3)
	*AUC (h*ng/mL)*	32.1	28.3 ± 6.3
Rosuvastatin	C_{max} *(ng/mL)*	27.7	25.9 ± 18.77
	T_{max} *(h)*	4.40	3.91 ± 3.73
	*AUC (h*ng/mL)*	255.6	210.2 ± 178.70

Ex vivo data was incorporated into a generic PBPK model and simulations resulted in relatively accurate predictions of the plasma concentration (Area Under the Curve (AUC)), plasma peak concentration (C_{max}), hepatic clearance and bioavailability when compared to human clinical studies

CONCLUSIONS

The combination of ex vivo gut, liver and kidney models with a generic PBPK model is a unique and powerful combination to predict ADME profile of (new) drugs

- possibility to calculate the fraction that undergoes enterohepatic circulation.
- Future research is aimed at studying drug-drug interactions an the effects of disease processes.