COMBINED EX VIVO LIVER AND KIDNEY PERFUSION TO PREDICT BILIARY AND RENAL CLEARANCE

TNO HEALTHY LIVING

TNO initiates technological and societal innovation for healthy living and a dynamic society.

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TNO innovation for life

INTRODUCTION

- Good prediction of the absorption, distribution, metabolism and excretion (ADME) profile of drugs is of high importance in the drug development process. However, this is often hampered by the lack of translational in vitro and in vivo models. Therefore, robust translational models are needed which can help predict the, hepatic clearance (metabolic and biliary) and renal clearance of compounds

Solution

- Ex vivo whole organ models, are a promising tool compared to in vitro models as bile and urine samples can be generated

- Normothermic perfusion of slaughterhouse porcine liver and kidney to predict biliary and renal clearance. Simultaneous perfusion of the liver and kidney will

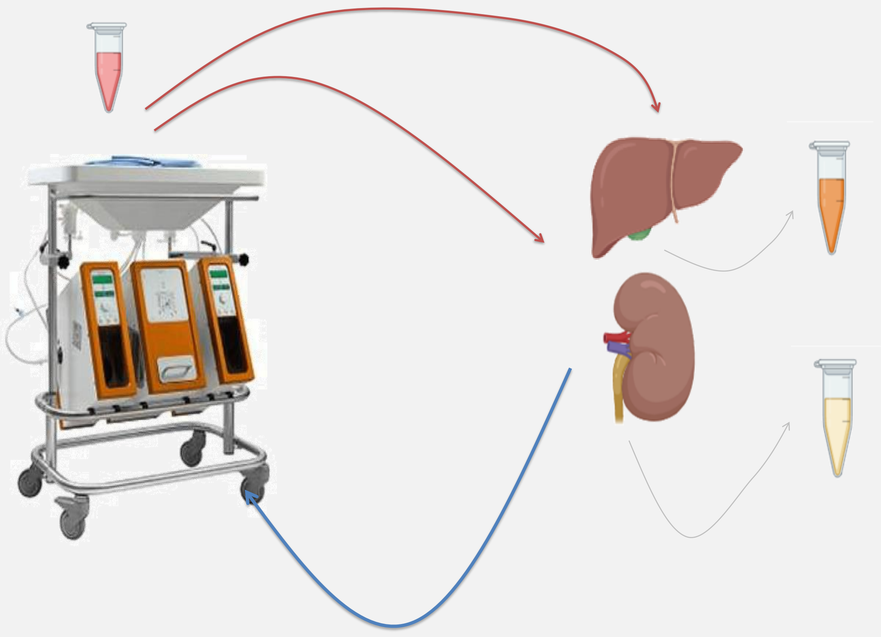

***Figure** 1. Graphical representation of combined ex vivo liver and kidney perfusion; generating perfusate, bile and urine fractions.*

- Clearance of model compounds ICG and inulin

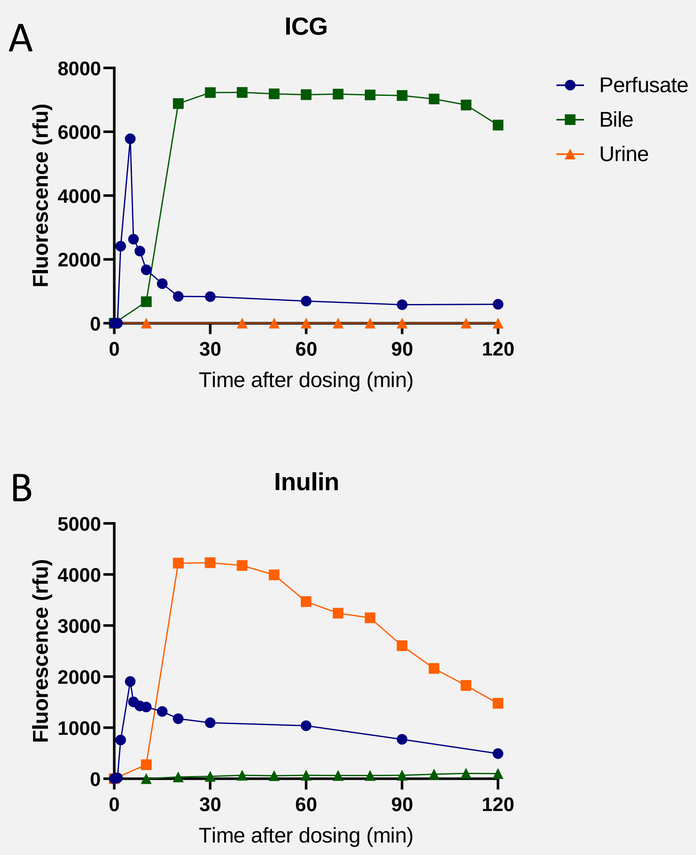

***Figure 2**. Hepatic and renal clearance of fluorescently labelled model compounds ICG (hepatic and biliary clearance) and inulin (renal and urinary clearance). (A) ICG is excreted into bile and not into urine (B) inulin excretion into urine and not into bile*

Hepatic, renal, biliary & urinary clearance

Model compounds digoxin, rosuvastatin, metformin and rosuvastatin

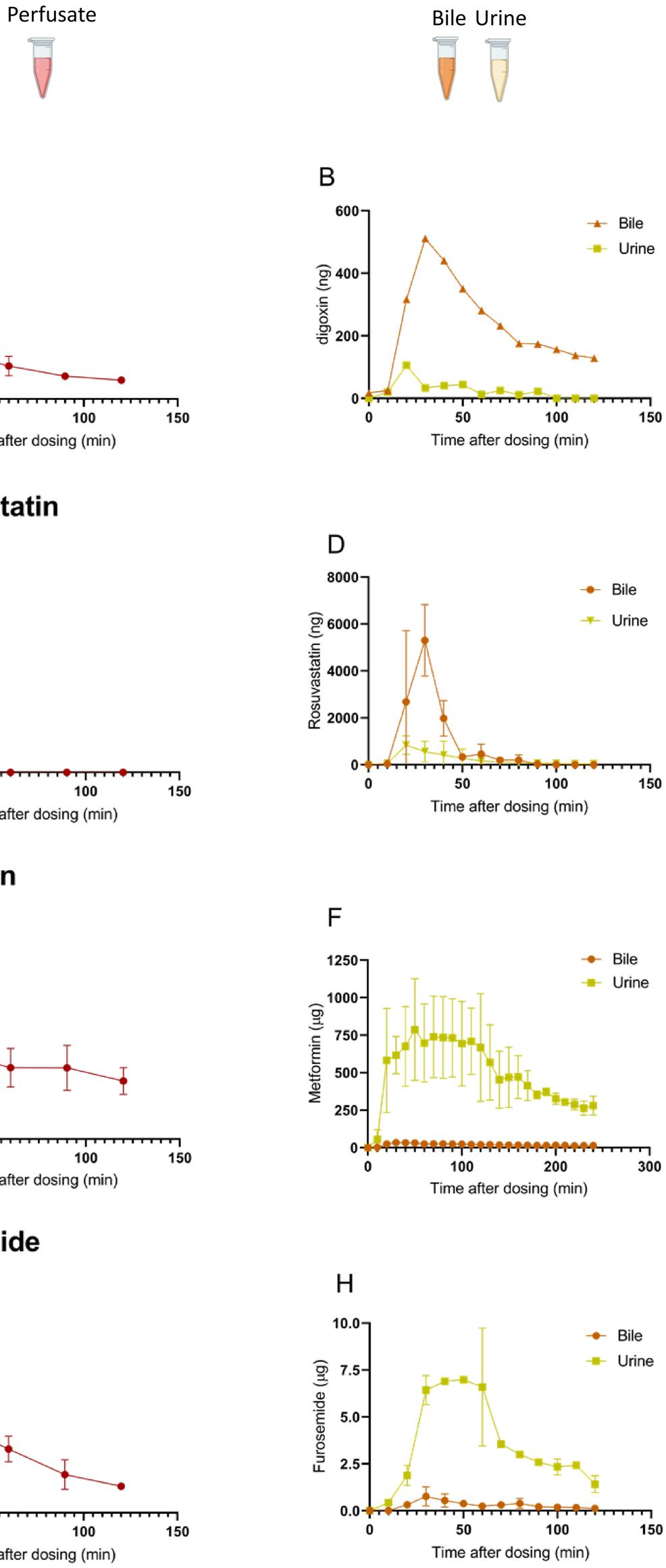

***Figure 3**. Hepatic, renal, biliary and urinary clearance profiles of 4 model drugs during ex vivo normothermic liver and kidney perfusion. Perfusate clearance profiles and biliary and urinary excretion profiles are shown for (A-B) digoxin, (C-D) rosuvastatin, (E-F) Metformin and (G-H) Furosemide*

YOUR BENEFITS

- Biliary and urinary excretion of compound of interest determined in one experiment by making use of human-like organs

- Possibility to combine with intestinal absorption studies and PBPK modelling
  - to predict ADME profile of (new) drug
  - to calculate the fraction that undergoes enterohepatic circulation