Drug interactions through uptake and efflux transport systems in the liver: implications for cellular pharmacokinetics of competing drugs

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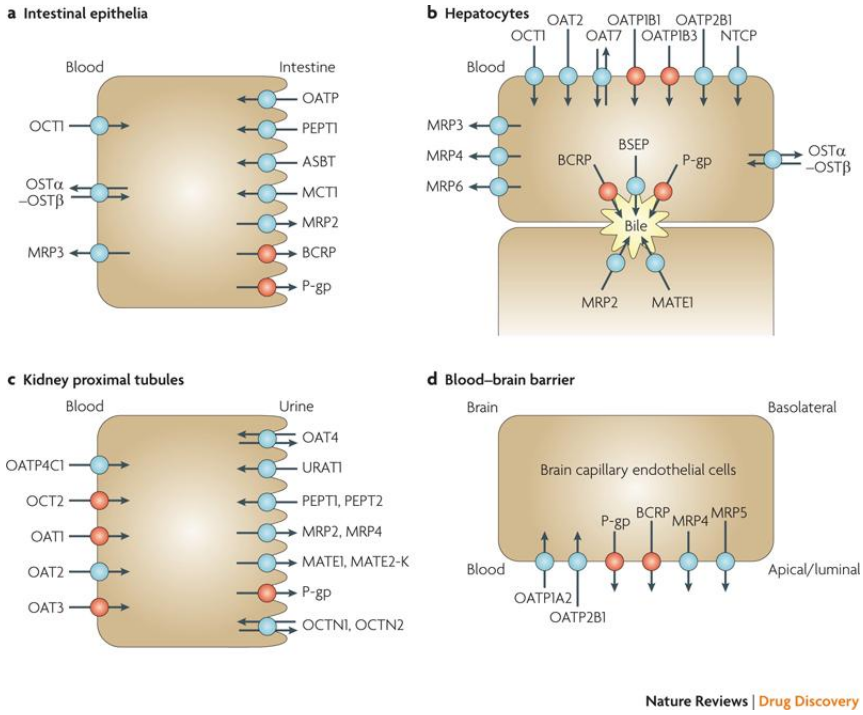
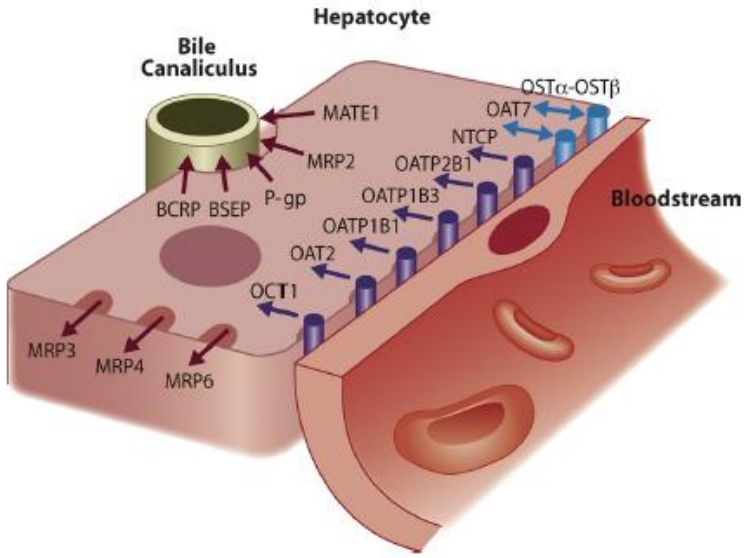
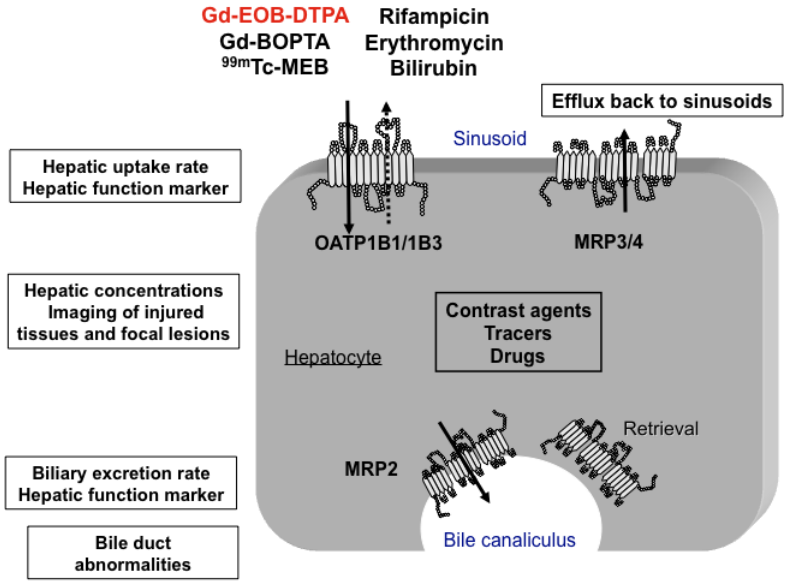
Membrane transporters and drugs

- Recent information on the interaction of drugs and metabolites with transporters present in membranes of various cells
- An International Transporter Consortium (ITC) was formed to identify transporters important for the pharmacokinetics of drugs and to characterize drug-transporter interactions
- En 2012, new guidelines (EMA and FDA) on investigation of drug interactions according to transporter systems



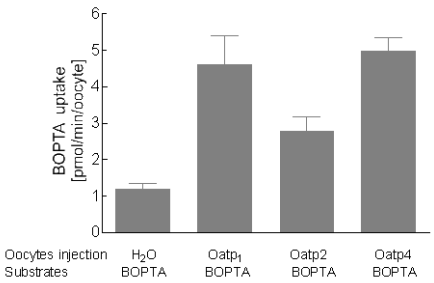


M Niemi, Pharmacol Rev, 2011, 63, 157



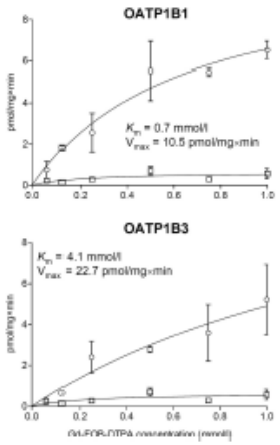
Uptake of contrast agents through OATPs

Gd-BOPTA
Rat transporters



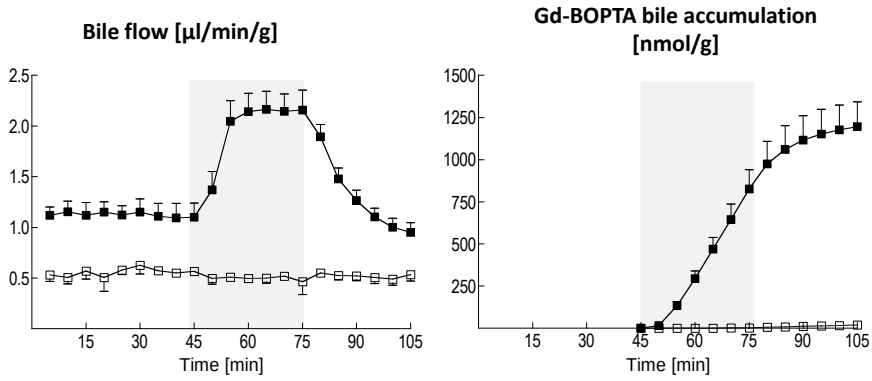
CM Pastor, 2007, Mol Pharmacol, 71, 1089

Gd-EOB-DTPA
Human transporters



M Leonhardt, 2010, DMD, 38, 1024

Gd-BOPTA bile excretion through Mrp2

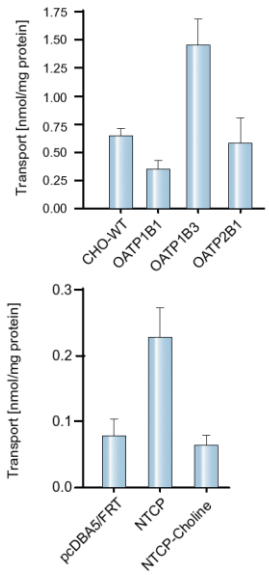


Perfused livers associated from normal rats (□) or rats without Mrp2 (□)

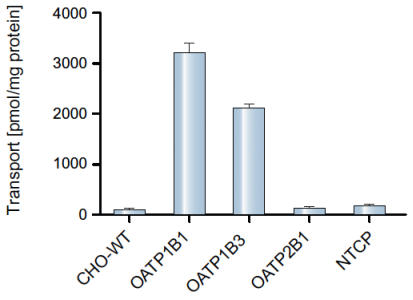
CM Pastor, JPET, 2011, 336, 624

Dyes and tracers uptake through OATPs

ICG



^{99m}Tc-MEB



Bruno Stieger, 2011, J Hepatol, 54, 738

Alterations of drug transport through OATPs-MRP2

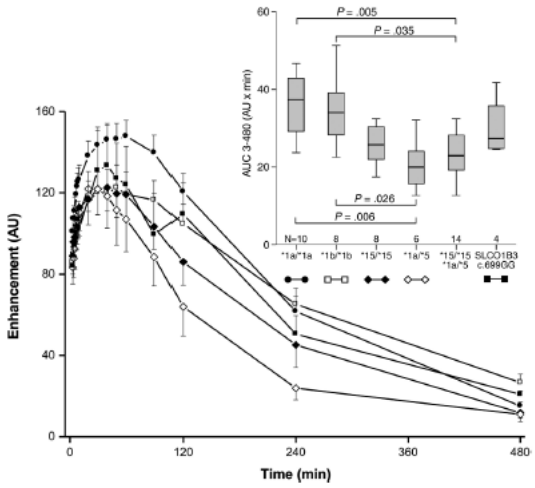
- Genetic polymorphism that modifies drug distribution in normal subjects (liver)
- Human diseases that change the expression and function of transporters: focal lesions and cirrhosis
- Drug-drug interactions (or competitions between drugs that have similar transport pathway)

Alterations of drug transport through OATPs-MRP2

- **Genetic polymorphism that modifies drug distribution in normal subjects**

Signal intensities-time and AUC of Gd-EOB-DTPA to functional relevant genotypes of *SLCO1B1* and *SLCO1B3.*

Volunteers
Gd-EOB-DTPA injection
Signal intensities or estimation of intrahepatic concentrations over 480 min



Nassif A, Radiology, 2012, 264, 741

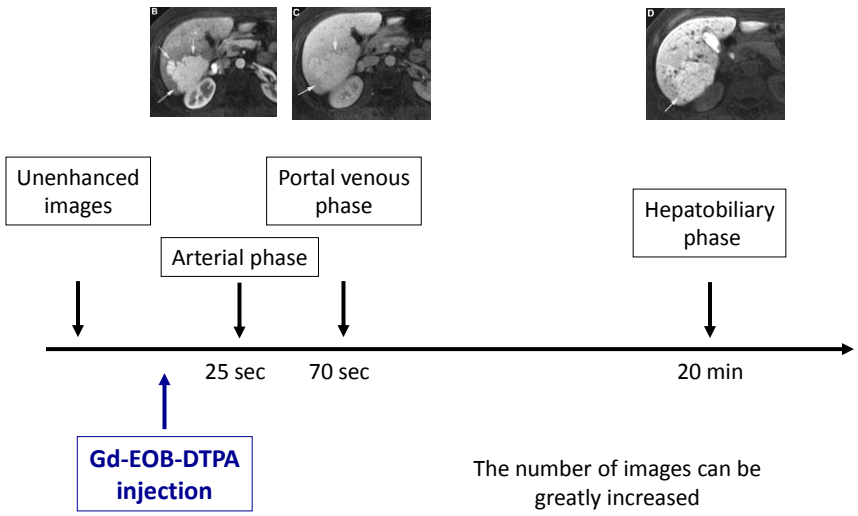
Alterations of drug transport through OATPs-MRP2

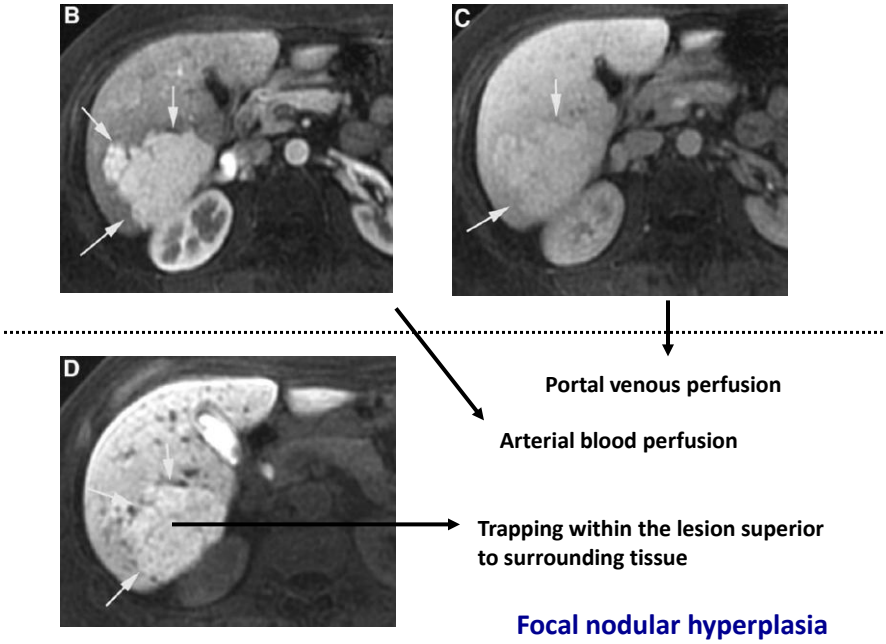
- Genetic polymorphism that modifies drug distribution in normal subjects
- **Human diseases that change the expression and function of transporters: focal lesions and cirrhosis**
- Drug-drug interactions (or competitions between drugs that have similar transport pathway)

Alterations of drug transport through OATPs-MRP2

- Human diseases that change the expression and function of transporters: **focal lesions**

MRI with the contrast agent Gd-EOB-DTPA



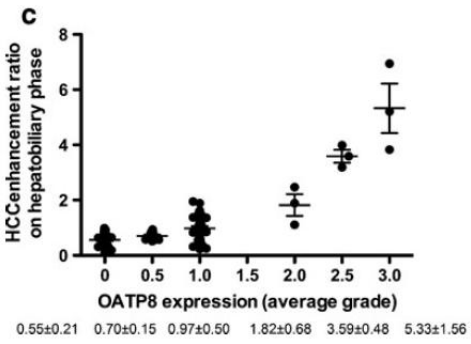


Gd-EOB-DTPA uptake in hepatocellular carcinomas

EOB-MRI vs. OATP1B3

Radiology

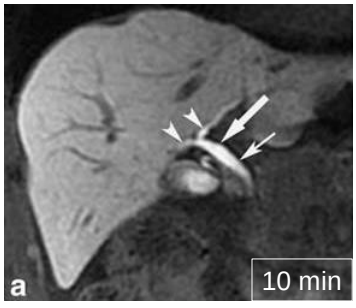
Tsuboyama T, 2010, 255:824

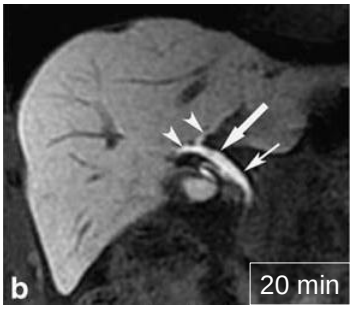


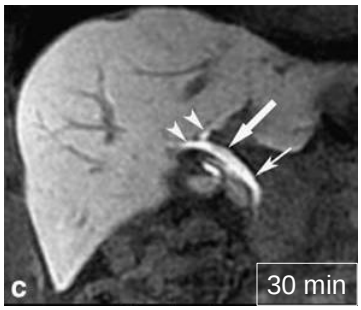
A Kitao, Eur Radiol 2011 21, 2056

Alterations of drug transport through OATPs-MRP2

- Human diseases that change the expression and function of transporters: **cirrhosis**

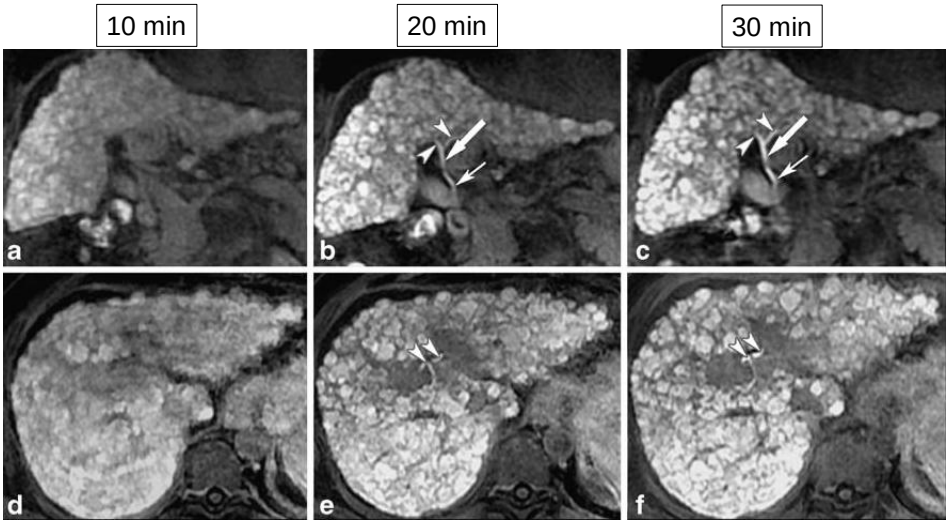






Liver MRI following Gd-EOB-DTPA injection

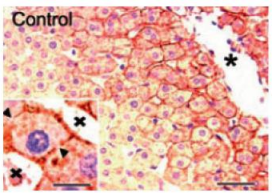
Normal liver



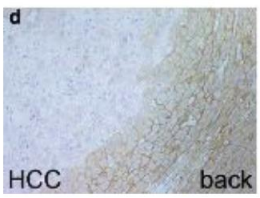
F Tschirch, Eur Radiol, 2008, 18,1577

Clinical project: radiology CHUV

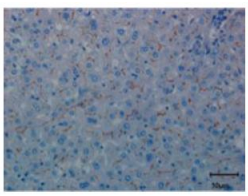
- Volunteers and cirrhotic patients
- MRI with Gd-EOB-DTPA
- Transjugular liver biopsies
- Pathology: METAVIR and Laennec scores
- OATP1B1/B3 and MRP2 expression by immunohistochemistry



OATP1B1



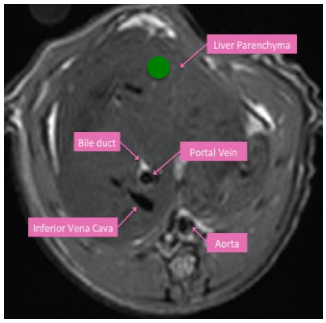
OATP1B3



MRP2

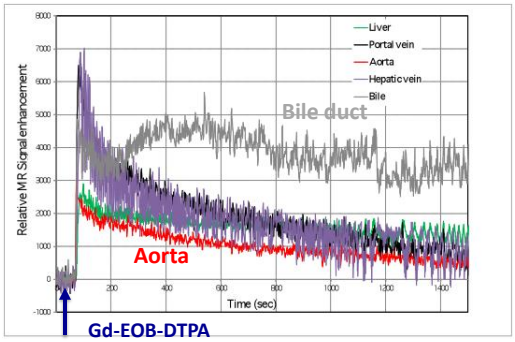
Clinical and experimental collaboration: radiology CHU Beaujon

ROI in the liver



Visualization of rat liver anatomy (IRM 7 Tesla)

Measurements of signal intensities in ROI over time



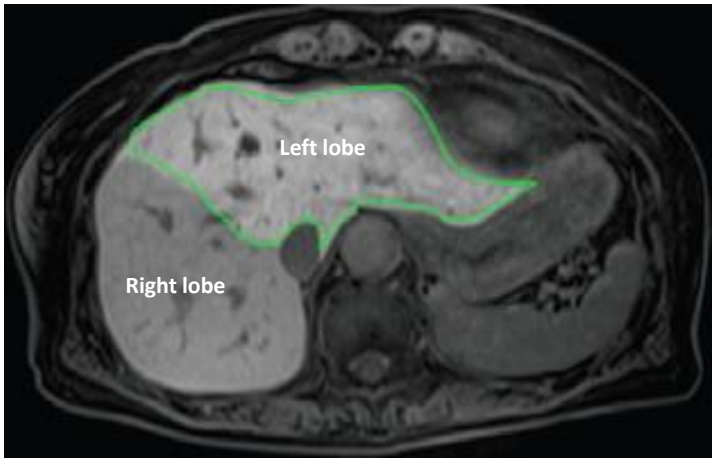
Pharmacokinetics of Gd-EOB-DTPA in liver, portal vein, aorta, hepatic vein, and bile duct

Parameters of pharmacokinetics and compartmental analysis

Alterations of drug transport through OATPs-MRP2

- Human diseases that change the expression and function of transporters: **evaluation of hepatic function**

Patient with hilar bile duct carcinoma
Portal vein embolization (right branch)
Decreased SI in the right hepatic lobe



Hepatic uptake with ^{99m}Tc-MEB

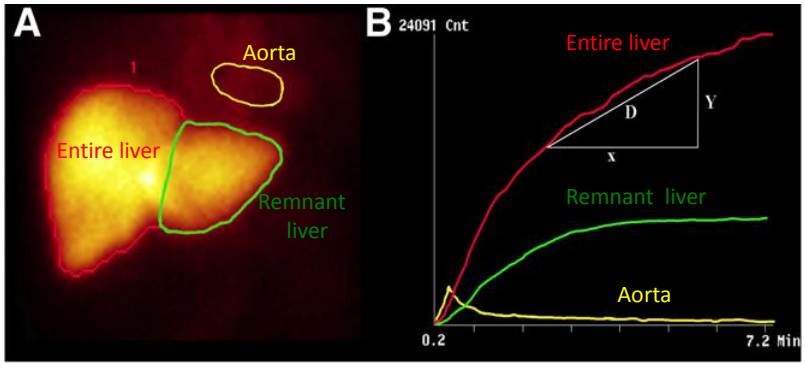
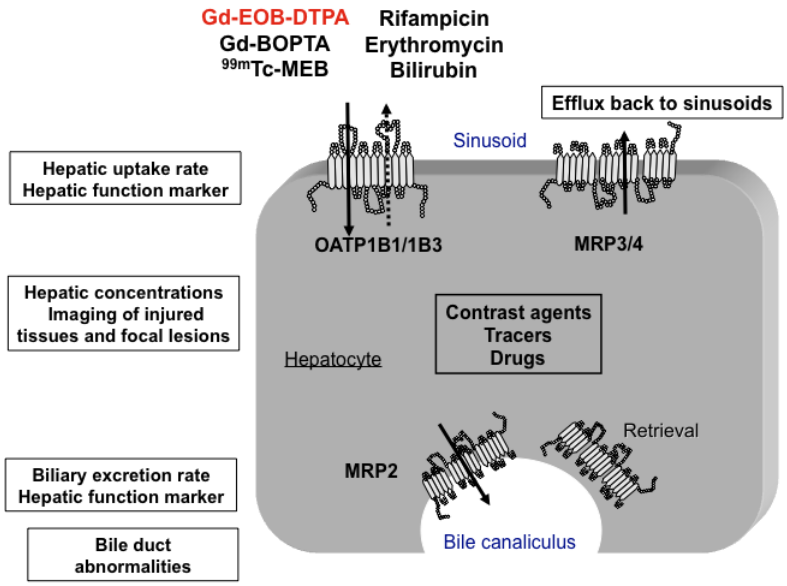


FIGURE 2. Dynamic image of planar HBS. (A) Example of summed HBS images from 150 to 350 s after intravenous injection of ^{99m}Tc-mebrofenin. ROI is drawn around entire liver (red line), mediastinum (blood pool; yellow line), and FRL (green line). (B) Blood-pool–corrected liver uptake time–activity curve. Liver uptake of mebrofenin is calculated as increase of blood-pool–corrected ^{99m}Tc-mebrofenin uptake (*y*-axis) per minute over a period of 200 s.

W de Graaf, JNM, 2010, 51, 274

Alterations of drug transport through OATPs-MRP2

- Genetic polymorphism that modifies drug distribution in normal subjects
- Human diseases that change the expression and function of transporters: focal lesions and cirrhosis
- **Drug-drug interactions (or competitions between drugs that have similar transport pathway)**



Importance of hepatic concentrations of drugs

- In liver imaging, images correlate to **hepatic concentrations of contrast agents and tracers**
- Cell concentrations are important for **drugs acting within hepatocytes** (statins)
- **Metabolism of drugs depends on hepatic concentrations** (metabolizing enzymes-transport interplay)

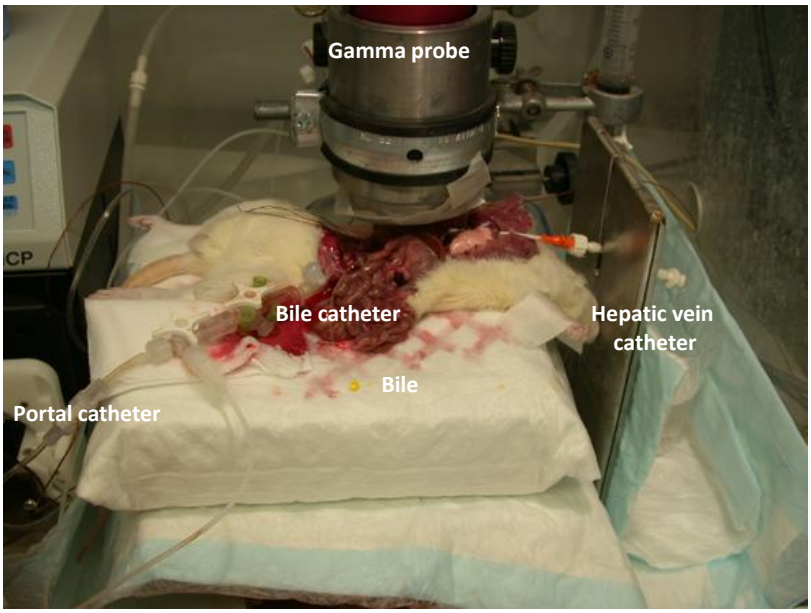
Hepatic concentrations of drugs

- Apart from liver imaging with contrast agents and tracers, the hepatocellular pharmacokinetics is difficult to assess in humans
- We developed a new model to investigate drug-drug interactions through uptake and efflux transport systems

….. **The isolated and perfused rat liver**

Why using isolated and perfused rat livers?

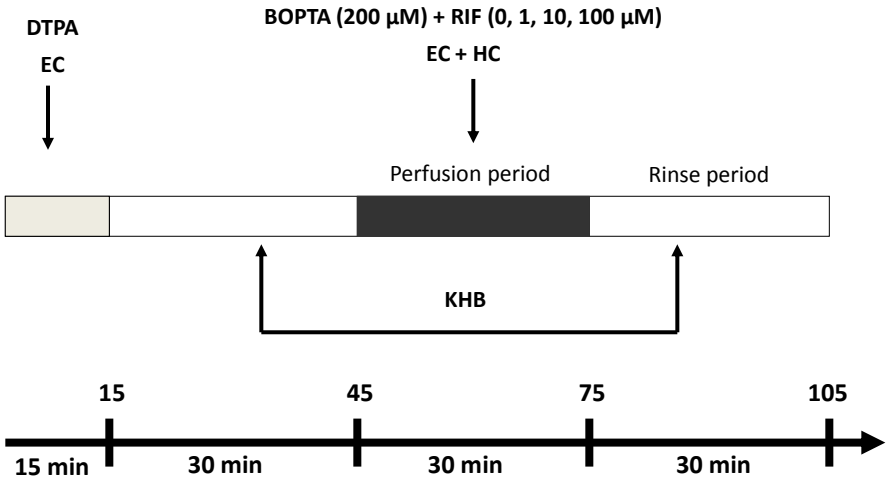
- Easy to control hepatic perfusate flow (set by a pump)
- Composition of perfused solutions well controlled
- Interference with extrahepatic organs avoided by liver isolation
- The same protocols are applied over time for competing drugs alone and then drug-drug can be evaluated in similar experimental conditions



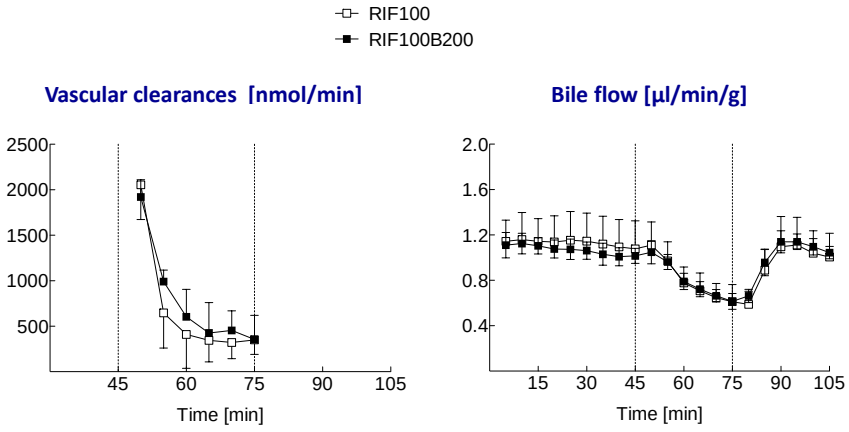
Evidence of drug-drug interactions through uptake and efflux transport systems in rat hepatocytes: implications for cellular concentrations of competing drugs

DMD, 2013 in press

Gd-BOPTA and rifampicin transport et interactions in rat liver



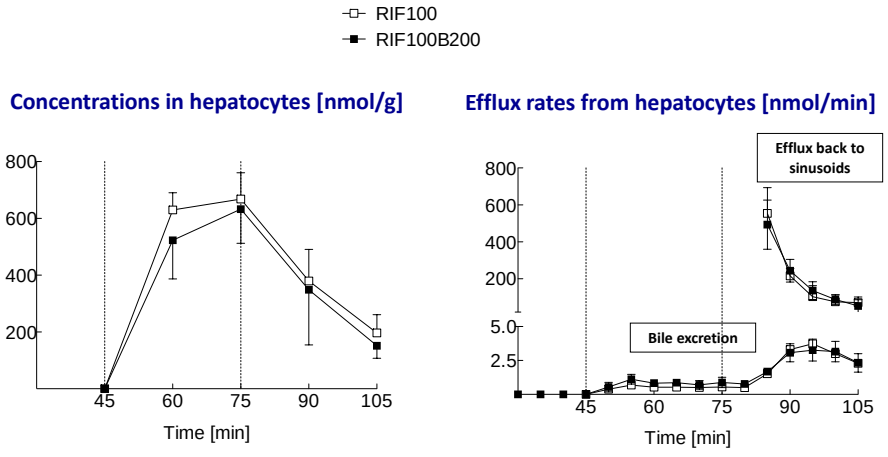
Rifampicin transport



100 µM Rifampicin = 3000 nmol/min

200 µM Gd-BOPTA = 6000 nmol/min

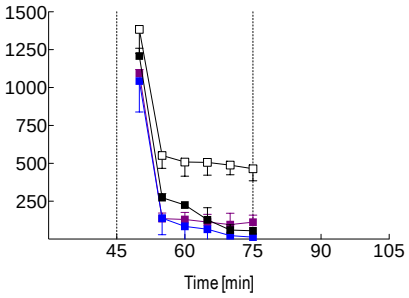
Rifampicin transport



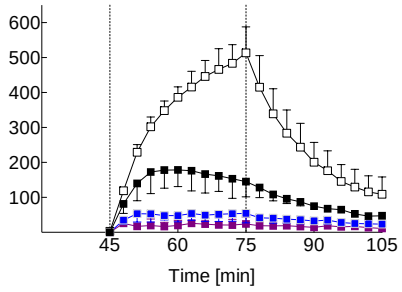
Gd-BOPTA transport

B200
B200R100
B200R10
B200R1

Vascular clearances [nmol/min]



Concentrations in hepatocytes [nmol/g]



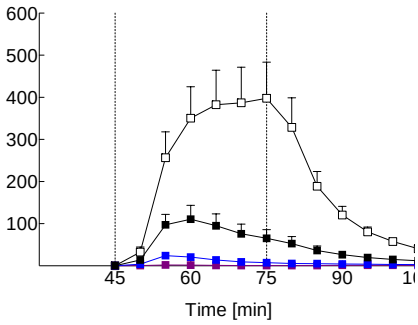
100 µM Rifampicin = 3000 nmol/min

200 µM Gd-BOPTA = 6000 nmol/min

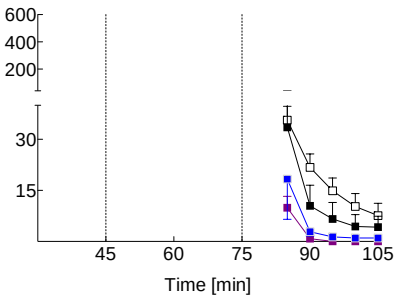
Gd-BOPTA transport

B200
B200R100
B200R10
B200R1

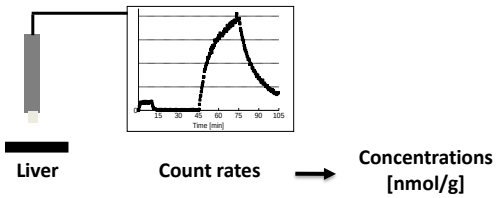
Bile excretion rate [nmol/min]



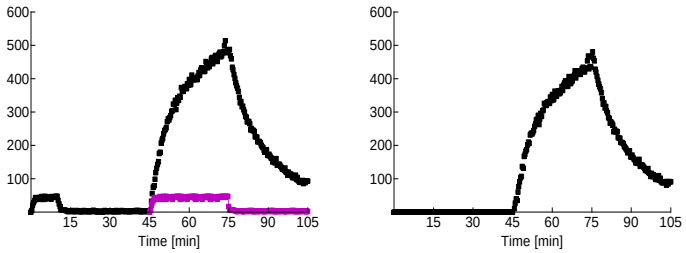
Perfusate efflux back [nmol/min]



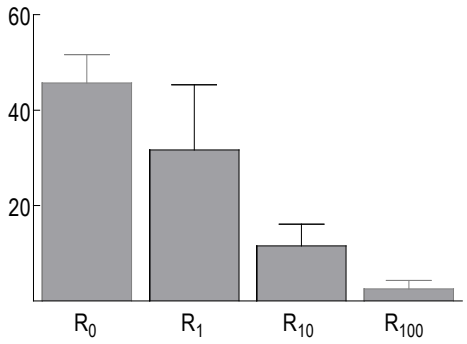
A. On line recording of ^{153}Gd-DTPA and ^{153}Gd-BOPTA count rates



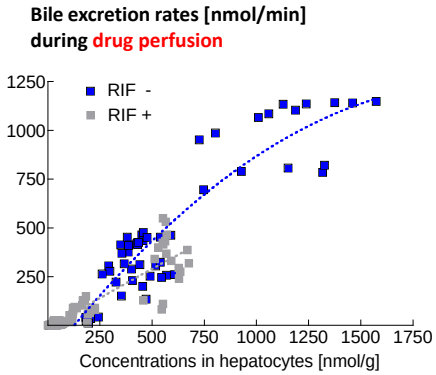
B and C. Hepatic concentrations [nmol/g]

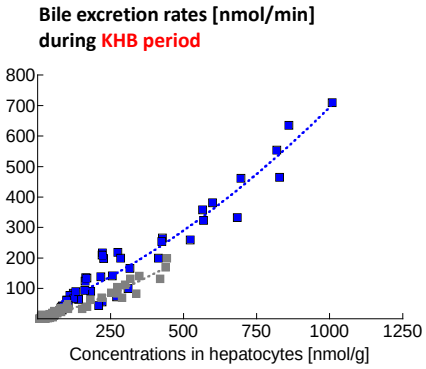


Initial hepatic uptake index [nmol/min/g]

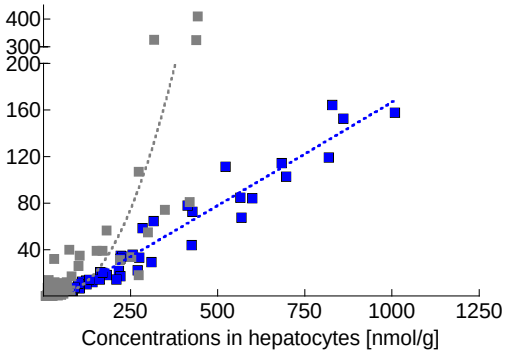


Cellular efflux vs. hepatic concentrations through canalicular transporters





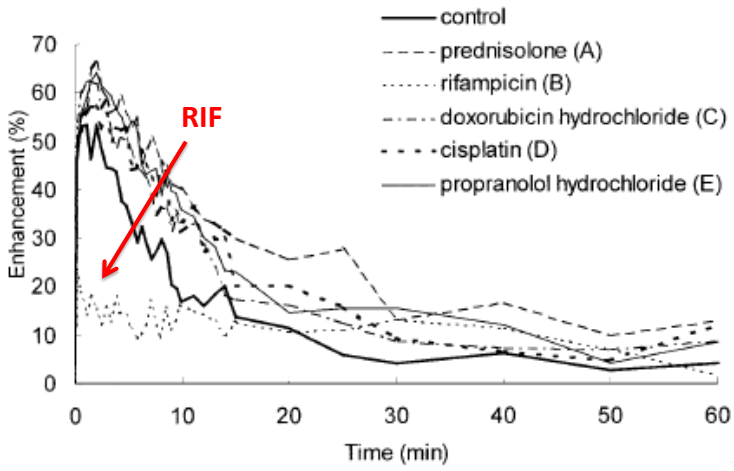
Cellular efflux [nmol/min] vs. hepatic concentrations [nmol/g] through sinusoidal transporters



Conclusions

- Information obtained in IPRL > DDI by vascular clearances
- RIF (100 µM) is cholestastic
- RIF is eliminated from hepatocytes by efflux back to the circulation
- RIF decreases the bile excretion of endogenous compounds
- BOPTA is a choleretic drug eliminated from hepatocytes mainly by bile excretion
- RIF decreases BOPTA uptake into hepatocytes according to concentrations
- RIF increases the efflux rates of BOPTA from hepatocytes back to the circulation

Drug-drug interactions: Gd-EOB-DTPA and RIF (MRI in rats)



N Kato, Investigative Radiology, 2002, 37, 680

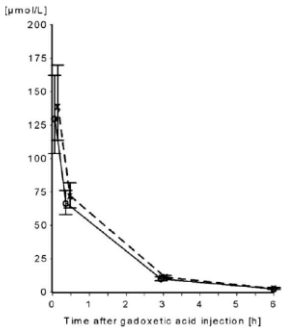
No interaction between Gd-EOB-DTPA and erythromycin in patients

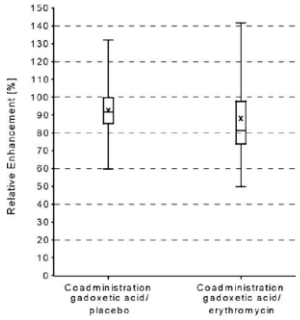
JOURNAL OF MAGNETIC RESONANCE IMAGING 33:409–416 (2011)

Original Research

Evaluation of Possible Drug–Drug Interaction Between Gadoxetic Acid and Erythromycin as an Inhibitor of Organic Anion Transporting Peptides (OATP)

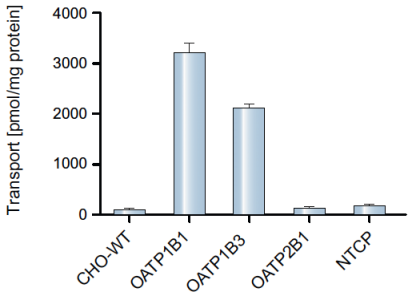
Alexander Huppertz, MD,[1,2]* Josy Breuer, MD,[3] Lueder M. Fels, PhD,[4] Marcus Schultze-Mosgau, PhD,[4] Gabriele Sutter, PhD,[4] Stefan Klein, PhD,[3] Bernd Frericks, MD,[1] Bernd Hamm, MD,[1] and Moritz Wagner, MD[1]





Complexity of hepatic drug-drug interactions!

^{99m}Tc-MEB

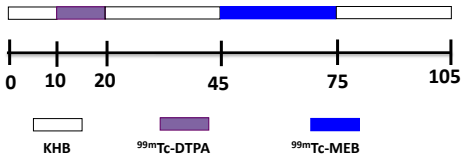


Preliminary data
^{99m}Tc-MEB and rifampicin

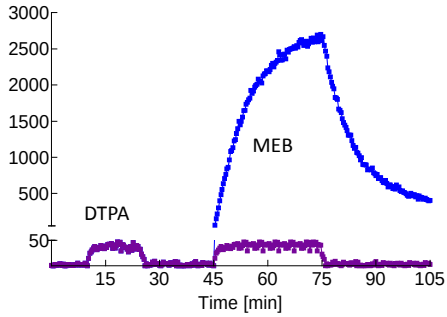
^{99m}Tc-DTPA and ^{99m}Tc-Mebrofenin transport

Perfusion solutions

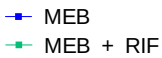
DTPA: 64 µM
MEB: 64 µM



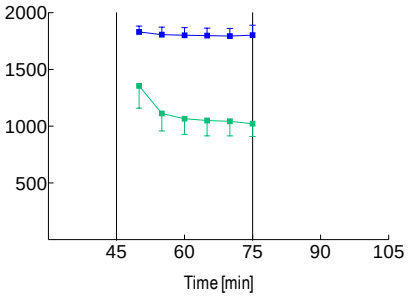
Hepatic concentrations [nmol/g] (gamma probe)



^{99m}Tc-MEB transport

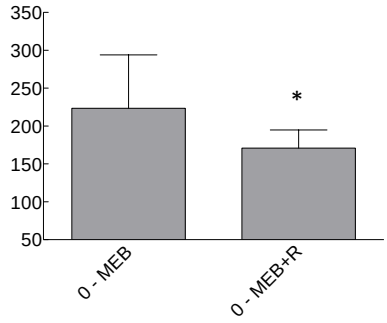


Vascular clearances [nmol/min]



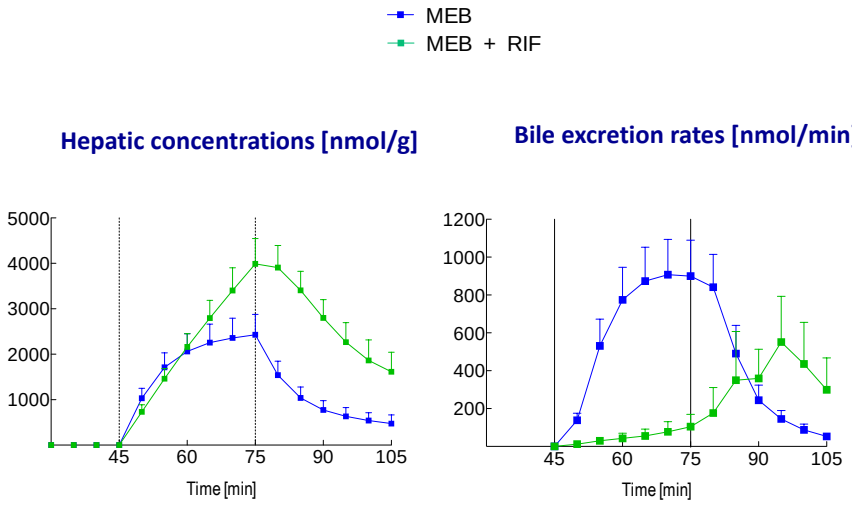
100 µM Rifampicin = 3000 nmol/min

IHUI [nmol/min/g]

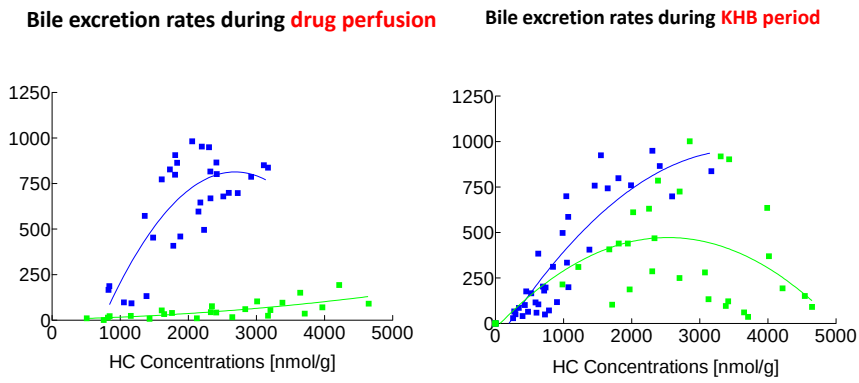


64 µM ^{99m}Tc-MEB = 1920 nmol/min

^{99m}Tc-MEB transport



Cellular efflux vs. hepatic concentrations through canalicular transporters



Interaction between MEB and RIF

- RIF decreases initial uptake rate of MEB
- RIF is eliminated mainly by efflux back to sinusoids
- RIF blocks Mrp2 and MEB bile excretion and increases MEB hepatic concentrations
- When RIF leaves cells, MEB bile excretion can recover

…. **the method is an interesting tool to understand the complexity of drug-drug interactions …**

Conclusion

- OATPs transport a broad number of compounds that compete to enter into hepatocytes
- These competitions are complex as shown in perfused rat livers
- Such interactions might impair liver enhancements at MRI
- Besides the interest for imaging, drug-drug interactions and transporter-mediated hepatic pharmacokinetics is an important issue in pharmacology

Drug Metabolism Reviews, 2010, 1–12, Early Online

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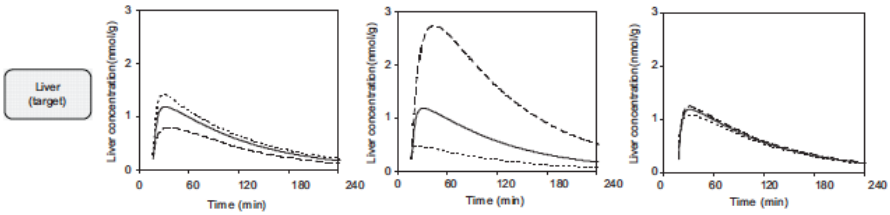
REVIEW ARTICLE

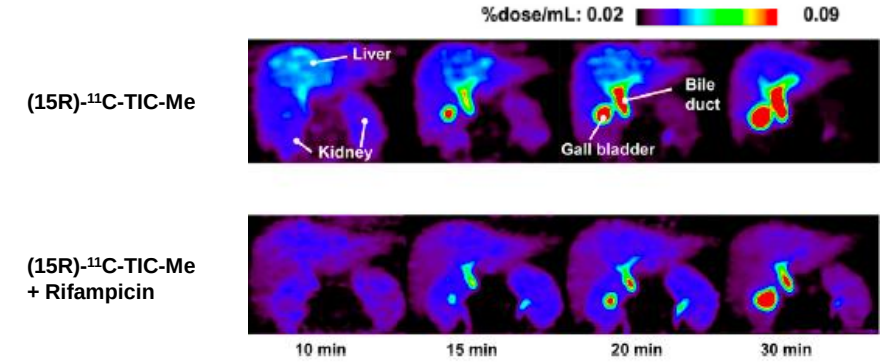
Pharmacokinetic modeling of the hepatobiliary transport mediated by cooperation of uptake and efflux transporters

Hiroyuki Kusuhara, and Yuichi Sugiyama



PET Imaging–Based Evaluation of Hepatobiliary Transport in Humans with (15*R*)-^{11}C-TIC-Me

Tadayuki Takashima[1,2], Satoshi Kitamura[3], Yasuhiro Wada[1,2], Masaaki Tanaka[2], Yoshihito Shigihara[2], Hideki Ishii[1,2], Ryosuke Ijuin[1,2], Susumu Shiomi[2], Takahiro Nakae[1], Yumiko Watanabe[1], Yilong Cui[1], Hisashi Doi[1], Masaaki Suzuki[1], Kazuya Maeda[3], Hiroyuki Kusuhara[3], Yuichi Sugiyama[3], and Yasuyoshi Watanabe[1,2]



Thank you for your attention

Many thanks to Pierre Bonnaventure and Youssef Daali