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

Catherine M PASTOR, MD, PhD
catherine.pastor@hcuge.ch

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-EOB-DTPA
Rifampicin
Erythromycin
Bilirubin

Efflux back to sinusoids

Hepatic uptake rate
Hepatic function marker

Hepatic concentrations
Imaging of injured tissues and focal lesions

Biliary excretion rate
Hepatic function marker

Bile duct abnormalities

M Leonhardt, 2010, DMD, 38, 1024

CM Pastor, 2007, Mol Pharmacol, 71, 1089

Gd-BOPTA
Rat transporters

OATP1B1/1B3
MRP3/4

OATP1B3

Human transporters

OATP1B1

Km = 0.1 mmol/l
Vmax = 0.5 pmol/mg.min

OATP1B3

Km = 4.1 mmol/l
Vmax = 22.7 pmol/mg.min

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

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 \textit{SLCO1B1} and \textit{SLCO1B3}.

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

\begin{figure}
\centering
\includegraphics[width=\textwidth]{signal_intensities_time_auc}
\caption{Signal intensities-time and AUC of Gd-EOB-DTPA to functional relevant genotypes of \textit{SLCO1B1} and \textit{SLCO1B3}.}
\end{figure}


\section*{Alterations of drug transport through OATPs-MRP2}

- Genetic polymorphism that modifies drug distribution in normal subjects
- \textbf{Human diseases that change the expression and function of transporters: focal lesions and cirrhosis}
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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

Unenhanced images → Portal venous phase → Arterial phase → Hepatobiliary phase

- Gd-EOB-DTPA injection

25 sec → 70 sec → 20 min

The number of images can be greatly increased
Gd-EOB-DTPA uptake in hepatocellular carcinomas

EOB-MRI vs. OATP1B3
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
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
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

Gd-BOPTA and rifampicin transport et interactions in rat liver
**Rifampicin transport**

**Vascular clearances [nmol/min]**

![Graph showing vascular clearances](image)

**Bile flow [µl/min/g]**

![Graph showing bile flow](image)

100 µM Rifampicin = 3000 nmol/min

200 µM Gd-BOPTA = 6000 nmol/min

**Rifampicin transport**

**Concentrations in hepatocytes [nmol/g]**

![Graph showing concentrations in hepatocytes](image)

**Efflux rates from hepatocytes [nmol/min]**

![Graph showing efflux rates from hepatocytes](image)

Efflux back to sinusoids

Bile excretion
**Gd-BOPTA transport**

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**

Bile excretion rate [nmol/min]

Perfusate efflux back [nmol/min]
A. On line recording of $^{153}\text{Gd-DTPA}$ and $^{153}\text{Gd-BOPTA}$ count rates

B and C. Hepatic concentrations [nmol/g]

Initial hepatic uptake index [nmol/min/g]
Cellular efflux vs. hepatic concentrations through canalicular transporters

Bile excretion rates [nmol/min] during drug perfusion

Concentrations in hepatocytes [nmol/g]

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

Concentrations in hepatocytes [nmol/g]
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

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

Alexander Hupfertz, MD,1,2,*, Joey Braun, MD,2 Lueder M. Fels, PhD,2 Marcus Schultz-Mosgau, PhD,1,2 Gabriela Sutter, PhD,1 Stefan Klein, PhD,1 Berni Frendel, MD,1 Berni Herren, MD,1 and Mario Wagner, MD1

Complexity of hepatic drug-drug interactions!

Preliminary data 99mTc-MEB and rifampicin
**99mTc-DTPA and 99mTc-Mebrofenin transport**

**Perfusion solutions**

DTPA: 64 µM  
MEB: 64 µM

**Hepatic concentrations [nmol/g] (gamma probe)**

**99mTc-MEB transport**

**Vascular clearances [nmol/min]**

**IHUI [nmol/min/g]**

100 µM Rifampicin = 3000 nmol/min  
64 µM 99mTc-MEB = 1920 nmol/min
**Hepatic concentrations [nmol/g]**

**Bile excretion rates [nmol/min]**

**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
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 (15R)-11C-TIC-Me

Tadayuki Takashima1,2, Satoshi Kitamura3, Yasuhiro Wada1,2, Masaaki Tanaka2, Yoshihito Shigihara2, Hideki Ishii1,2, Ryosuke Ijiri1,2, Susumu Shiom1, Takahiro Naka1, Yumiko Watanabe1, Yikong Cui2, Hisashi Doi1, Masaaki Suzuki1, Kazuya Maeda3, Hiroyuki Kusuhara1, Yukichi Sugiyama2, and Yasuyoshi Watanabe1,2

(15R)-11C-TIC-Me

(15R)-11C-TIC-Me + Rifampicin
Thank you for your attention

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