Drug Interactions, Transporter - Mediated

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Drug transporters: déjà vu all over again

Back to the future....
A paper of mine almost no one knows about

High affinity uptake by isolated rat hepatocytes of a linear pseudo-hexapeptide, ditekiren

Richard B. Kim *, Pat R. Perry, Grant R. Wilkinson

Department of Pharmacology, Vanderbilt University, Nashville, TN 37232-6600, USA

Received 13 March 1997; accepted 19 March 1997
Ditekiren, a Renin Inhibitor started My Interest in Drug Transporters

![Graph](image)

**Fig. 4.** Induction of ditekiren uptake in hepatocytes derived from rats pretreated with phenobarbital. Mean data ± S.E. of total uptake at 37°C (●) and 4°C (▲) and carrier-mediated uptake (○).

**Acknowledgements**

This work was supported in part by U.S. Public Health Service grant GM 31304. Assistance in obtaining the oligopeptides used in the study is greatly appreciated: Drs. M.J. Ruwart and G.J. Szpunar (The Upjohn Co.); Drs. H.P. Faro and H. Wurziger (E. Merck, Darmstadt) and Dr. M.L. Foehg (Henri Beau- four Institute).
Renin Inhibitors: nearly two decades later...

One did make it to market
Jan 2011: Aliskiren Looked Great

Aliskiren and the calcium channel blocker amlodipine combination as an initial treatment strategy for hypertension control (ACCELERATE): a randomised, parallel-group trial

Morris J Brown, Gordon T McInnes, Cheraz Cherif Papst, Jack Zhang, Thomas M MacDonald

Interpretation We believe that routine initial reduction in blood pressure (>150 mm Hg) with a combination such as aliskiren plus amlodipine can be recommended.

Funding Novartis Pharma AG.

“The Novartis hypertension franchise is now DOA, obviously.

Furthermore, this class of DRIs has died with the death of this drug.”

Novartis announced today the early termination of the ALTITUDE trial, which was testing the effect of the direct renin inhibitor aliskiren (Rasilez, Tekturna) in type 2 diabetics at high risk for cardiovascular and renal events. The action was based on the recommendation of the independent Data Monitoring Committee (DMC), after it found an increased risk for non-fatal stroke, renal complications, hyperkalemia, and hypotension in patients taking aliskiren after 18-24 months. Patients in ALTITUDE were randomized to receive aliskiren or placebo in addition to an ACE inhibitor or an angiotensin receptor blocker (ARB).

The company is also recommending that physicians not prescribe drugs containing aliskiren with either an ACE inhibitor or an ARB. Patients who are already taking a combination pill should be switched to an alternative anti-hypertensive regimen, according to the company.

The action represents a major setback for a drug that had once been thought to have blockbuster potential. Novartis said it was immediately ceasing all promotion of products containing aliskiren and was talking with health authorities about the implications of the findings.

Aliskiren was first approved in 2007 for the treatment of hypertension. Novartis said that total sales for Rasilez and Tekturna were $449 million for the first 9 months of 2011.
What Works: another protease inhibitor

HIV PIs
The Drug Transporter P-glycoprotein Limits Oral Absorption and Brain Entry of HIV-1 Protease Inhibitors

Richard B. Kim, Martin F. Fromm, Christoph Wandel, Brenda Leake, Alastair J.J. Wood, Dan M. Roden, and Grant R. Wilkinson

Division of Clinical Pharmacology, Departments of Medicine and Pharmacology, Vanderbilt University School of Medicine, Nashville, Tennessee 37232-6602

0021-9738/98/01/0289/06 $2.00
Volume 101, Number 2, January 1998, 289–294
http://www.jci.org
PHARMACOLOGICAL INHIBITION OF P-GLYCOPROTEIN TRANSPORT ENHANCES THE DISTRIBUTION OF HIV-1 PROTEASE INHIBITORS INTO BRAIN AND TESTES

EDNA F. CHOO, BRENDA LEAKE, CHRISTOPH WANDEL, HITOSHI IMAMURA, ALASTAIR J. J. WOOD, GRANT R. WILKINSON, AND RICHARD B. KIM

CHO0 ET AL.

[Graph showing brain/plasma and testes/plasma ratios with various treatments and their effects on the ratios.]
If you are targeting liver...

You have to know liver transporters (especially OATPs)
Hepatic Drug Transporters
# Hepatic OATP Transporters

<table>
<thead>
<tr>
<th>OATP1B1</th>
<th>OATP1B3</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>(OATP-C, LST-1, OATP2)</strong></td>
<td><strong>(OATP8, LST-2)</strong></td>
</tr>
<tr>
<td><strong>Endogenous Substrates:</strong></td>
<td><strong>Endogenous Substrates:</strong></td>
</tr>
<tr>
<td>Estrone Sulfate, PGE$_2$, Bilirubin, thyroid hormone (T$_3$, T$_4$) Bilirubin-glucuronides Estradiol 17β-d-glucuronide, bile acids</td>
<td>CCK-8, PGE$_2$ Thyroid hormone (T$_3$, T$_4$) Estradiol 17β-d-glucuronide, Bile acids, Deltorphin, DPDPE,</td>
</tr>
<tr>
<td><strong>Drug Substrates:</strong></td>
<td><strong>Drug Substrates:</strong></td>
</tr>
<tr>
<td>Atorvastatin, Cerivastatin, Pravastatin</td>
<td>Pravastatin, Pitavastatin, Rosuvastatin,</td>
</tr>
<tr>
<td>Rosuvastatin, Pitavastatin, Caspofungin, Troglitazone-sulfate, Rifampin, Arsenic, Atrasentan, Valsartan, Olmesartan, Enalapril, MTX, Temocaprilat, SN-38</td>
<td>Fexofenadine, BQ-123, Oubain, Digoxin, Doxorubicin, Paclitaxel, Rifampin, MTX, Bilirubin, Repaglinide, Telmisartan, Valsartan, Olmesartan, Enalapril, Temocaprilat, SN-38</td>
</tr>
<tr>
<td><strong>Toxins:</strong></td>
<td><strong>Toxins:</strong></td>
</tr>
<tr>
<td>Phalloidin, Microcystin-LR</td>
<td>Phalloidin, Microcystin-LR</td>
</tr>
</tbody>
</table>
Drug and Bile Acid Transporters in Rosuvastatin Hepatic Uptake: Function, Expression, and Pharmacogenetics

RICHARD H. HO,*Ⅱ ROMMEL G. TIRONA,ⅡⅡ BRENDA F. LEAKE,ⅡⅡⅡ HARTMUT GLAESER,ⅡⅡⅡ
WOOIN LEE,ⅡⅡ CHRISTOPHER J. LEMKE,ⅡⅡⅡ YI WANG,* and RICHARD B. KIMⅡⅡⅡ

*Department of Pediatrics, ⅡDepartment of Medicine, and ⅡDepartment of Pharmacology, Vanderbilt University Medical Center, Nashville, Tennessee; and *Drug Metabolism and Pharmacokinetics, AstraZeneca, Wilmington, Delaware
We found the rosuvastatin transporters
Then we found human NTCP is also involved (very cool)
We show why gemfibrozil does not cause a huge rosvastatin DDI
Also, if you are targeting the liver, OATP1B1 may be better than OATP1B3.
Knockout Mice Data
ACCELERATED COMMUNICATION

Targeted Disruption of Murine Organic Anion-Transporting Polypeptide 1b2 (oatp1b2/S/col1b2) Significantly Alters Disposition of Prototypical Drug Substrates Pravastatin and Rifampin

Hani Zaher, Henriette E. Meyer zu Schwabedissen, Rommel G. Tirona, Melissa L. Cox, Leslie A. Obert, Nidhi Agrawal, Joe Palandra, Jeffrey L. Stock, Richard B. Kim, and Joseph A. Ware

Pfizer Global Research and Development, Ann Arbor, Michigan (H.Z., J.P., M.L.C., L.A.O., N.A., J.A.W.) and Groton, Connecticut (J.L.S.); Division of Clinical Pharmacology, Department of Medicine, and Department of Physiology and Pharmacology, The University of Western Ontario, London, Ontario, Canada (H.E.M.z.S., R.G.T., R.B.K.); Lawson Health Research Institute, London, Ontario, Canada (R.B.K.)

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Oatp1b2 KO mice

A

anti-Oatp1b2
anti-calnexin

B

Slco1b2-wildtype

C

Slco1b2−/−

D

E

Graph showing comparison of rilampin levels in liver/plasma ratio between wildtype and Slco1b2−/− mice.
In vivo human relevance
Functional Polymorphisms in OATP1B1 (OATP-C)

Polymorphisms in OATP-C

IDENTIFICATION OF MULTIPLE ALLELIC VARIANTS ASSOCIATED WITH ALTERED TRANSPORT ACTIVITY AMONG EUROPEAN- AND AFRICAN-AMERICANS

Received for publication, April 27, 2001, and in revised form, June 28, 2001
Published, JBC Papers in Press, July 26, 2001, DOI 10.1074/jbc.M103792200

Rommel G. Tirona, Brenda F. Leake, Gracia Merino, and Richard B. Kim

From the Division of Clinical Pharmacology, Departments of Medicine and Pharmacology, Vanderbilt University School of Medicine, Nashville, Tennessee 37232-6602
Identification of SNPs in OATP1B1

OATP1B1 SNPS and Statin PK and Toxicity

- hydrophilic “statin”
- OATP1B1, OATP2B1 substrate
- high liver distribution
- uptake rate-limited
- wide interindividual variability
- not metabolized
Impact of OATP1B1 Haplotypes to Pravastatin Pharmacokinetics

Pravastatin AUC (ng•hr/mL)

- *1b/1b: 67
- *1a/1b: 90
- *1a/1a: 87
- *1a/5: 59
- *1b/15: 100
- *1a/15: 121*
- *15/15: 167*

OATP1B1 Genotype

- 388
- 521

- *1a
- *1b
- *5

Ho RH et al., Pharmacogenetics Genomics 17:647-656, 2007
# Transporter SNPs and Statin Exposure

<table>
<thead>
<tr>
<th>Transporter Genotype</th>
<th>OATP1B1</th>
<th>BCRP</th>
<th>Change in HMG-CoA Reductase Inhibitor Area-Under-The-Curve</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Lovastatin</td>
<td>Simvastatin Acid</td>
<td>Pravastatin</td>
</tr>
<tr>
<td>521 TC</td>
<td>?</td>
<td>– 1.2-fold</td>
<td>– 1.3-fold</td>
</tr>
<tr>
<td>521 CC</td>
<td>?</td>
<td>– 3.2-fold</td>
<td>– 2-fold</td>
</tr>
</tbody>
</table>

- Nishizato et al., Clin Pharmacol Ther 2003
- Niemi et al., Pharmacogenetics 2004
- Mwinyi et al., Clin Pharmacol Ther 2004
- Lee et al., Clin Pharmacol Ther 2005
- Zhang et al., Clinica Chimica Acta 2006
- Pasanen et al., Pharmacogenet Genomics 2006
- Niemi et al., Clin Pharmacol Ther 2006
- Maeda et al., Clin Pharmacol Ther 2006
- Pasanen et al., Clin Pharmacol Ther 2007
- Ho et al., Pharmacogenet Genomics 2007

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Figure 1. Results of Tests for a Trend in the Association between Myopathy and Each SNP Measured in the Genomewide Association Study.

P values are shown for each SNP measured among 85 participants with myopathy and 90 matched controls who were taking 80 mg of simvastatin daily. Analyses are based on 316,184 of the 318,237 SNPs (99.4%) on the Sentrix HumanHap300-Duo BeadChip (Illumina). A result above the horizontal red line indicates strong evidence of an association (P<5×10^{-7}).
The genetic defect turned out to be one my group had first identified in 2001.
OATP1B1 has a day time job....

Inhibition of hepatic OATPs and disease risk
Hepatic Organic Anion Transporting Polypeptide Transporter and Thyroid Hormone Receptor Interplay Determines Cholesterol and Glucose Homeostasis

Henriette E. Meyer zu Schwabedissen,1 Joseph A. Ware,3,8 David Finkelstein,4 Amarjit S. Chaudhry,5 Sara Lemay,1 Matilde Leon-Ponte,1 Stephen C. Strom,6 Hani Zaher,3 Ute I. Schwarz,1,2 David J. Freeman,2 Erin G. Schuetz,5 Rommel G. Tirona,1,2 and Richard B. Kim1,2

Meyer zu Schwabedissen H.E. et al Hepatology 2011
Oatp1b2 KO mice have lower Cyp7a1, Dio1, and Pepck.

Meyer zu Schwabedissen H.E. et al Hepatology 2011
Oatp1b2 KO mice have reduced glucose tolerance

Meyer zu Schwabedissen H.E. et al Hepatology 2011
Glut2 transporter expression is lower in Oatp1b2 KO mice

Meyer zu Schwabe-Diissen H.E. et al Hepatology 2011
Human liver samples: OATP1B1 predicts GLUT2 expression

Meyer zu Schwabedissen H.E. et al Hepatology 2011
OATP1B1 and TR activation and glucose homeostasis

- **OATP1B1**
- **TR activation**
- **Glucose homeostasis**

**Glucose output**
- Glucose
- Gluconeogenesis
- Glycogenolysis

**Glucose uptake**
- Insulin
- **GLUT2**

**Gene transcription**
- **LDL-R**
- **Cyp7a1**

**Cholesterol**
- Bile acids

**Glucose**
- **GK**
- **G6P**
- Glycolysis
- **GLUT2**

**OATP1B**
- **T4**
- **T3**
- **Oatp1b2**

**T3**
- **TRβ**

**Insulin**
- **GK**
- **G6P**

**T4**
- **DIO1**
- **Cyp7a1**

**LDL-R**
- **Cholesterol**
Regulation of OATP1B1

Not PXR or CAR
Liver X Receptor $\alpha$ and Farnesoid X Receptor Are Major Transcriptional Regulators of OATP1B1

Henriette E. Meyer zu Schwagedissen, Kerstin Böttcher, Amarjit Chaudhry, Heyo K. Kroemer, Erin G. Schuetz, and Richard B. Kim

HEPATOLOGY, November 2010
FXR and LXR agonists induce OATP1B1 in human hepatocytes
What would be the clinical phenotype when OATP1B1 and 1B3 are inhibited??

Look for conjugated hyperbilirubinemia
Rotor Syndrome

- Autosomal recessive
- Rare: 1 in a million
- Jaundice (hyperbilirubinemia)
- Conjugated hyperbilirubinemia
- Elevated urine coproporphyrin
Rotor Syndrome: Deficient in both OATP1B1 and 1B3

Van de Steeg et al JCI, 122:519-528, 2012
Rotor Syndrome: Phenotype-Conjugated Hyperbilirubinemia

Van de Steeg et al JCI, 122:519-528, 2012
Summary

• Drugs that attain high liver:plasma ratio likely use hepatic uptake transporters such as OATP1B1/1B3
• Inhibition of OATPs may account for some of the DDIs seen with drugs that require hepatic uptake.
• Functional OATP SNPs may result in reduced hepatic concentration, while increasing systemic exposure for substrate drugs.
• Activation of nuclear receptors likely account for some of the PK changes seen with DDIs.