

# DRUG METABOLISM AND DISPOSITION

A Publication of the American Society for Pharmacology and Experimental Therapeutics

August 2007

Vol. 35, No. 8

## CONTENTS

### SHORT COMMUNICATIONS

- A Natural Variant of the Heme-Binding Signature (R441C) Resulting in Complete Loss of Function of CYP2D6. *Kathrin Klein, Stephan Tatzel, Sebastian Raimundo, Tanja Saussele, Elisabeth Hustert, Jürgen Pleiss, Michel Eichelbaum, and Ulrich M. Zanger* . . . . . **1247**

- Frequency of the Frame-Shifting CYP2D7 138delT Polymorphism in a Large, Ethnically Diverse Sample Population. *Anahita Bhathena, Toby Mueller, David R. Grimm, Ken Idler, Alan Tsurutani, Brian B. Spear, and David A. Katz* . . . . **1251**

### ARTICLES

- UDP-Glucuronosyltransferase 1A1 Gene Polymorphisms and Total Bilirubin Levels in an Ethnically Diverse Cohort of Women. *Andrew L. Hong, Dezheng Huo, Hee-Jin Kim, Qun Niu, Donna L. Fackenthal, Shelly A. Cummings, Esther M. John, Dee W. West, Alice S. Whittemore, Soma Das, and Olufunmilayo I. Olopade* . . . . **1254**

- Interaction of Positional Isomers of Quercetin Glucuronides with the Transporter ABCC2 (cMOAT, MRP2). *Gary Williamson, Isabelle Aeberli, Laurence Miguet, Ziding Zhang, M.-Belen Sanchez, Vanessa Crespy, Denis Barron, Paul Needs, Paul A. Kroon, H. Glavinas, Peter Krajcsi, and Martin Grigorov* . . . . . **1262**

- Identification of Metabolites of 4-Nonylphenol Isomer 4-(3',6'-Dimethyl-3'-Heptyl) Phenol by Rat and Human Liver Microsomes. *Xiaoyun Ye, Amber M. Bishop, Larry L. Needham, and Antonia M. Calafat* . . . . . **1269**

- Asymmetric Intestinal First-Pass Metabolism Causes Minimal Oral Bioavailability of Midazolam in Cynomolgus Monkey. *Tomohiro Nishimura, Nobuyuki Amano, Yoshiyuki Kubo, Midori Ono, Yukio Kato, Hisashi Fujita, Yoshiaki Kimura, and Akira Tsuji* . . . . . **1275**

- The Use of Microdialysis for the Study of Drug Kinetics: Central Nervous System Pharmacokinetics of Diphenhydramine in Fetal, Newborn, and Adult Sheep. *Sam C.S. Au-Yeung, K. Wayne Riggs, Nancy Gruber, and Dan W. Rurak* . . . . **1285**

- Comparative Metabolic Capabilities and Inhibitory Profiles of CYP2D6.1, CYP2D6.10, and CYP2D6.17. *Hongwu Shen, Minxia M. He, Houfu Liu, Steven A. Wrighton, Li Wang, Bin Guo, and Chuan Li* . . . . . **1292**

- Cytochrome P450 3A-Dependent Metabolism of a Potent and Selective  $\gamma$ -Aminobutyric Acid<sub>A $\alpha$ 2/3</sub> Receptor Agonist in Vitro: Involvement of Cytochrome P450 3A5 Displaying Biphasic Kinetics. *Bennett Ma, Stacey L. Polsky-Fisher, Stanley Vickers, Donghui Cui, and A. David Rodrigues* . **1301**

- Substrate-Dependent Drug-Drug Interactions between Gemfibrozil, Fluvastatin and Other Organic Anion-Transporting Peptide (OATP) Substrates on OATP1B1, OATP2B1, and OATP1B3. *Johannes Noé, Renée Portmann, Marie-Elise Brun, and Christoph Funk* . . . . . **1308**

- Atorvastatin Glucuronidation Is Minimally and Nonselectively Inhibited by the Fibrates Gemfibrozil, Fenofibrate, and Fenofibric Acid. *Theunis C. Goosen, Jonathan N. Bauman, John A. Davis, Chongwoo Yu, Susan I. Hurst, J. Andrew Williams, and Cho-Ming Loi* . . . . . **1315**

Continued on next page

Saturable Uptake of Lipophilic Amine Drugs into Isolated Hepatocytes: Mechanisms and Consequences for Quantitative Clearance Prediction. <i>David Hallifax and J. Brian Houston</i> . . . . .	<b>1325</b>	6-Hydroxybuspirone Is a Major Active Metabolite of Buspirone: Assessment of Pharmacokinetics and 5-Hydroxytryptamine <sub>1A</sub> Receptor Occupancy in Rats. <i>Harvey Wong, Randy C. Dockens, Lori Pajor, Suresh Yeola, James E. Grace, Jr., Arlene D. Stark, Rebecca A. Taub, Frank D. Yocca, Robert C. Zaczek, and Yu-Wen Li</i> . . . . .	<b>1387</b>
Expression of Thirty-six Drug Transporter Genes in Human Intestine, Liver, Kidney, and Organotypic Cell Lines. <i>Constanze Hilgendorf, Gustav Ahlin, Annick Seithel, Per Artursson, Anna-Lena Ungell, and Johan Karlsson</i> . . . . .	<b>1333</b>	The Role of Monocarboxylate Transporter 2 and 4 in the Transport of $\gamma$ -Hydroxybutyric Acid in Mammalian Cells. <i>Qi Wang and Marilyn E. Morris</i> . . . . .	<b>1393</b>
Central Nervous System Pharmacokinetics of the Mdr1 P-Glycoprotein Substrate CP-615,003: Intersite Differences and Implications for Human Receptor Occupancy Projections from Cerebrospinal Fluid Exposures. <i>Karthik Venkatakrishnan, Elaine Tseng, Frederick R. Nelson, Hans Rollema, , Jonathan L. French, Irina V. Kaplan, Weldon E. Horner, and Megan A. Gibbs</i> . . . . .	<b>1341</b>	Bosentan Is a Substrate of Human OATP1B1 and OATP1B3: Inhibition of Hepatic Uptake as the Common Mechanism of Its Interactions with Cyclosporin A, Rifampicin, and Sildenafil. <i>Alexander Treiber, Ralph Schneiter, Stephanie Häusler, and Bruno Stieger</i> . . . . .	<b>1400</b>
Metabolism, Distribution and Excretion of a Selective N-Methyl-D-Aspartate Receptor Antagonist, Traxoprodil, in Rats and Dogs. <i>Chandra Prakash, Donghui Cui, Michael J. Potchoiba, and Todd Butler</i> . . . . .	<b>1350</b>	Liquid Chromatography/Tandem Mass Spectrometry Detection of Covalent Binding of Acetaminophen to Human Serum Albumin. <i>Micaela C. Damsten, Jan N. M. Commandeur, Alex Fidder, Albert G. Hulst, Daan Touw, Daan Noort, and Nico P. E. Vermeulen</i> . . . . .	<b>1408</b>
Mutation of a Single Residue (K262R) in P450 2B6 Leads to Loss of Mechanism-Based Inactivation by Phencyclidine. <i>Mohamad Shebley and Paul F. Hollenberg</i> . . . . .	<b>1365</b>	Absorption, Distribution, Metabolism, and Elimination of the Direct Renin Inhibitor Aliskiren in Healthy Volunteers. <i>Felix Waldmeier, Ulrike Glaenzel, Bernard Wirz, Lukas Oberer, Dietmar Schmid, Michael Seiberling, Jessica Valencia, Gilles-Jacques Riviere, Peter End, and Sujata Vaidyanathan</i> . . . . .	<b>1418</b>
Mutational Analysis of a Highly Conserved Proline Residue in MRP1, MRP2, and MRP3 Reveals a Partially Conserved Function. <i>Isabelle J. Létourneau, Andrew J. Slot, Roger G. Deeley, and Susan P. C. Cole</i> . . . . .	<b>1372</b>	Human Organic Anion Transporters 1 (hOAT1/SLC22A6) and 3 (hOAT3/SLC22A8) Transport Edaravone (MCI-186; 3-methyl-1-phenyl-2-pyrazolin-5-one) and Its Sulfate Conjugate. <i>Naomi Mizuno, Tsuyoshi Takahashi, Yumiko Iwase, Hiroyuki Kusuvara, Takuro Niwa, and Yuichi Sugiyama</i> . . . . .	<b>1429</b>
Kinetics of Valproic Acid Glucuronidation: Evidence for in Vivo Autoactivation. <i>Harvey Wong, Vincent Tong, K. Wayne Riggs, Dan W. Rurak, Frank S. Abbott, and Sanjeev Kumar</i> . . . . .	<b>1380</b>	Impact of Physicochemical and Structural Properties on the Pharmacokinetics of a Series of $\alpha_1$ -Adrenoceptor Antagonists. <i>Alison Betts, Fidelma Atkinson, Iain Gardner, David Fox, Rob Webster, Kevin Beaumont, and Paul Morgan</i> . . . . .	<b>1435</b>

Supplemental material is available online at <http://dmd.aspetjournals.org>.

About the cover: Linkage disequilibrium (Lewontin's  $D'$ ) of 15 consecutive markers in *UGT1A1* in Caucasians (A) and African Americans (B). See the article by Hong et al. on page 1254 of this issue.