

## PI-145

DISTRIBUTION OF <sup>3</sup>H-DOMPERIDONE, A P-GLYCOPROTEIN (P-GP) SUBSTRATE, IN HEART STRUCTURES AND WHOLE-BODY TISSUES OF MDR1A (-/-) MICE. L. Couture, L. Nguyen, PhD, L. Tao, PhD, J. A. Nash, PhD, J. Turgeon, PhD, Faculty of Pharmacy, Université de Montréal, CTBR Bio-Research Inc, Montreal, PQ, Canada.

**BACKGROUND:** Block of voltage-gated cardiac K<sup>+</sup> channels and drug-induced Long QT syndrome have been reported with domperidone. We hypothesized that accumulation of domperidone in the heart could occur in the context of decreased activity of the ABC transporter P-gp (*mdr1a* (-/-)), thus leading to cardiac toxicity. The aim of our study was to determine whether distribution of domperidone to the heart is modulated by P-gp activity.

**METHODS:** Intravenous <sup>3</sup>H-domperidone was administered to *mdr1a* (+/+) and *mdr1a* (-/-) mice. Five animals/timepoint/strain were sacrificed at 6 different timepoints up to 120 min. post-dose. In 2 animals/timepoint/strain, tissues were excised and processed by liquid scintillation spectroscopy to determine radioactivity levels. Quantitative whole-body autoradioluminography (QWBA) was performed in 1 animal/timepoint/strain. Finally, metabolite profiling was obtained by HPLC/LCMS.

**RESULTS:** Radioactivity levels were higher in heart left and right ventricles of *mdr1a* (-/-) mice compared to *mdr1a* (+/+) animals, without any obvious difference in atriums. Other tissues including the brain, lungs and testis showed increased radioactivity levels in *mdr1a* (-/-) mice. Metabolite profiling analysis suggests a rapid metabolism of domperidone.

**CONCLUSIONS:** Our results suggest a role of P-gp in the extrusion of domperidone from the heart and other tissues. This indicates that P-gp may play an important role in the protection of cardiac tissues against xenobiotics.

## PI-146

EFFECTS OF INFANT FORMULA, COW MILK AND HUMAN MILK ON DRUG METABOLIZING ENZYMES. H. Xu, R. Rajesan, R. B. Kim, S. A. Kliever, B. Lonnerdal, P. A. Harper, M. Ho, J. W. Yun, J. Hutson, S. Ito, Hospital for Sick Children, Vanderbilt University School of Medicine, University of Texas Southwestern Medical Center, University of California, University of Toronto, Toronto, ON, Canada.

**BACKGROUND:** Caffeine, used for treating neonatal apnea, is eliminated 3-fold slower in breastfed infants than in formula-fed infants. Caffeine is metabolized by cytochrome P450 (CYP) 1A and CYP3A4, which are regulated by aryl hydrocarbon receptor (AhR) and pregnane X receptor (PXR) respectively. Here we hypothesized that formula but not human milk induces CYP1A and/or CYP3A4 via their regulatory pathways.

**METHODS:** Human milk samples from healthy lactating women were collected. Infant formula and cow milk were purchased. Lipid fraction of milk samples was obtained by organic extraction. mRNA and protein expression were measured by RT-PCR and western blotting. Reporter plasmids containing receptor response elements were tested for their activation.

**RESULTS:** CYP1A expression and AhR activity were induced by formula and cow milk but not by human milk. The AhR activation by formula was abolished by co-treatment of Ah antagonist. Formula and human milk also had differential effects on AhR activation by dibenz[a,h]anthracene, an AhR agonist. In addition, lipid fraction of formula but not human milk activated AhR. Both formula and human milk showed mild induction of CYP3A4 mRNA and PXR. However, co-transfection of hPXR did not increase PXR activation by milk treatments, suggesting a non PXR-mediated pathway.

**CONCLUSION:** Infant formula but not human milk contains AhR agonist(s) that induces CYP1A expression. Both infant formula and human milk induce CYP3A4 through non PXR-mediated pathway.

## PI-147

NO EFFECT OF AMOXICILLIN, DOXYCYCLINE, AND CIPROFLOXACIN ON THE PHARMACOKINETICS AND PHARMACODYNAMICS OF XIMELAGATRAN. H. Dorani, K. Schützer, T. Sarich, U. Wall, L. Ohlsson, U. Eriksson, AstraZeneca R&D Mölndal, AstraZeneca LP, Mölndal, Sweden.

**BACKGROUND:** The effects of amoxicillin, doxycycline, and ciprofloxacin on the pharmacokinetics and pharmacodynamics of melagatran after administration of oral ximelagatran were evaluated.

**METHODS:** Healthy volunteers (n=48) sequentially received two treatments: ximelagatran 36 mg as a single oral dose and, after a ≥2-day washout period, amoxicillin, doxycycline, or ciprofloxacin for Days 1 to 5 with a 36-mg dose of ximelagatran on Days 1 and 5.

**RESULTS:** The 90% confidence interval (CI) and least squares mean estimates for ximelagatran with/without the antibiotic as a single dose (Day 1) and at steady-state (Day 5) fell within the range demonstrating no interaction for area under the concentration-time curve (AUC) and maximum plasma concentration (C<sub>max</sub>) for amoxicillin and doxycycline. For ciprofloxacin, the 90% CI fell within the no-interaction range for AUC, but the lower limit for C<sub>max</sub> was slightly outside this range (0.68 versus 0.70) on Days 1 and 5. The mean time to C<sub>max</sub>, half-life, and renal clearance of melagatran did not differ as a function of whether ximelagatran was given with an antibiotic. None of the antibiotics affected melagatran-dependent prolongation of activated partial thromboplastin time. Co-administration of ximelagatran with the antibiotics was well tolerated.

**CONCLUSION:** The pharmacokinetics, pharmacodynamics, and tolerability of oral ximelagatran were not affected by amoxicillin, doxycycline, or ciprofloxacin.

## PI-148

LACK OF PHARMACOKINETIC INTERACTION BETWEEN NEBIVOLOL AND SPIRONOLACTONE. T. L. Morton, PhD, H. C. Tu, MS, S. Liu, MS, S. W. Chervenick, PhD, R. J. Rackley, PhD, M. Y. Huang, PhD, Mylan Pharmaceuticals Inc., Morgantown, WV.

**BACKGROUND:** To detect interaction between nebivolol (N), a unique cardioselective β-blocker shown to possess vascular endothelial nitric oxide releasing capabilities, and spironolactone by comparing pharmacokinetic (PK) parameters for spironolactone (S) and metabolites, canrenone (C) and 7α-thiomethyl spironolactone (TMS), in healthy subjects. This potassium-sparing diuretic (S) is used with β-blockers to treat CHF. Previously, S showed no effect on the PK of N.

**METHODS:** Thirty-six healthy subjects were enrolled, without regard to CYP2D6 genotype, in this open-label, randomized, one period study. Subjects received once-daily oral S (25 mg) on Days 1–10 and oral S (25 mg) plus N (10 mg) once-daily on Days 11–20. Blood samples were collected on Days 10 and 20 and prior to dosing on Days 8, 9, 18, and 19. Plasma concentrations of S, C and TMS were measured by LC/MS. Pharmacokinetic parameter estimates for S, C and TMS were compared by statistical analyses using 90% confidence intervals (CIs).

**RESULTS:** All treatments were well tolerated.

Analyte	C <sub>max</sub>		AUC <sub>T</sub>	
	Ratio	90% CI	Ratio	90% CI
S	1.06	0.95–1.19	0.95	0.90–1.02
C	1.04	1.00–1.09	1.05	1.03–1.08
TMS	1.19	1.10–1.29	1.14	1.07–1.20

**CONCLUSION:** Co-administration of N (10 mg) with S (25 mg) results in no clinically significant changes in the PK profile of S, C or TMS.