PI-119

TARIQUIDAR (TAR, XR-9576) SELECTIVELY INHIBITS P-GLYCOPROTEIN (P-GP) IN T-LYMPHOCYTES COMPARED TO THAT IN THE BLOOD-BRAIN BARRIER (BBB). M. Muszkat, MD, D. Kurnik, MD, G. G. Sofowora, MD, J. P. Donahue, PhD, G. R. Wilkinson, PhD, D.Sc., A. J. Wood, MD, Clinical Pharmacology and Medicine, Vanderbilt University, Nashville, TN.

BACKGROUND: Modulation of P-gp in humans has been hampered by the lack of potent and selective inhibitors. TAR does not have these limitations, thus, certain of its *in vivo* effects were investigated.

METHODS: A double-blind, placebo controlled study was performed in 9 healthy subjects following an initial dose-finding/safety study with oral loperamide (LOP). Intravenous TAR (150 mg over 30 min) or placebo was given on different days followed 30 min later by oral LOP (32 mg). Pupil diameter was determined prior to and every 30 min for 12 hr; serial plasma samples for measurement of LOP levels and the *ex vivo* efflux of the fluorescent dye $DiOC_2(3)$ were obtained over the same period.

RESULTS: TAR had no effect on LOP's plasma levels, however, it rapidly produced over 90% inhibition of P-gp mediated efflux of $DiOC_2(3)$ in T-lymphocytes that was maintained over the study period. Considerable interindividual variability in LOP's effect on the change in pupil diameter was observed which appeared to be related to the opioid's plasma level. Even in "responders", however, TAR did not change the extent of the pupillary effect.

CONCLUSIONS: Despite producing nearly complete inhibition of P-gp function in T-lymphocytes, TAR had negligible effect on the BBB and brain uptake of LOP. The reason(s) for such selectivity is unknown, but suggests that modulation of brain uptake of P-gp substrates may be more difficult than previous animal studies suggest.

PI-120

POPULATION PHARMACOKINETIC PROFILE OF MONTELUKAST IN CHILDREN AGED 3 TO 6 MONTHS WITH BRONCHIOLITIS. B. Knorr, MD, L. Maganti, PhD, R. Ramakrishnan, PhD, P. Larson, MS, C. A. Tozzi, PhD, T. F. Reiss, MD, Merck Research Laboratories, Rahway, NJ.

BACKGROUND: Bronchiolitis is a common respiratory disease in young children. Evidence suggests CysLTs are involved in its pathophysiology and treatment with montelukast (MNT) may be beneficial. Since there are no MNT pharmacokinetic (PK) data in children aged 3–6 months, the single-dose population estimate of $AUC_{(0\text{-}\infty)}$ (area under the concentration-time curve [AUC_{pop}]), maximum plasma concentration [C_{max}], and time to C_{max} [T_{max}] of MNT 4-mg oral granules were investigated. Data were compared to historical data in children aged 6–24 months.

METHODS: 14 children aged 3–6 months with active bronchiolitis or a history of bronchiolitis with "asthma-like" symptoms had plasma samples obtained and assayed for MNT after a single, oral 4-mg dose of MNT granules. Due to sparse sampling, a population PK approach with a nonlinear mixed-effect, 1-compartment model with first order absorption and elimination was used to fit the data. Ninety-five (95) % confidence intervals (CIs) for the AUC_{pop} ratio (3–6 months/6–24 months) were provided.

RESULTS: MNT 4-mg oral granules, in children aged 3–6 months, yielded systemic exposure (AUC_{pop}) (3644.3±481.5 ng•hr/mL) similar to that in children aged 6–24 months (3226.3± 250.0 ng•hr/mL), with an AUC_{pop} ratio of 1.13 [95% CI (0.83–1.55)]. Similarly, no clinically meaningful differences were seen for other PK parameters.

CONCLUSION: Systemic exposure after administration of 4-mg MNT oral granules is similar in children aged 3–6 months and 6–24 months.

PI-121

SINGLE-DOSE PHARMACOKINETICS AND ANTICOAGULANT ACTIVITY OF WARFARIN IS UNAFFECTED BY NEBIVOLOL IN HEALTHY VOLUNTEERS. T. E. Lawrence, PhD, S. Liu, MS, T. M. Bland, PhD, S. W. Chervenick, PhD, M. Y. Huang, PhD, R. J. Rackley, PhD, Mylan Pharmaceuticals Inc., Morgantown, WV.

BACKGROUND: Studies have reported that nebivolol possesses distinct nitric oxide releasing/vasodilating properties. The role of nitric oxide on endothelial and platelet function is well established in the literature. Given these actions, the effects of steady-state nebivolol on the pharmacokinetic (PK) and anticoagulant activity of warfarin were studied.

METHODS: This was an open-label study conducted in 12 healthy volunteers. Subjects were given a 10-mg dose of warfarin on Day 1 and Day 17. On Day 8-Day 22, 10 mg oral nebivolol was given QD. Blood samples for assessment of PK and anticoagulation (prothrombin time, INR) were taken at frequent intervals on Day 1 and Day 17.

RESULTS: Administration of nebivolol resulted in no clinically significant changes in the PK of R- or S-warfarin being observed (Table).

	C_{max}		$AUC_{0\text{-}\infty}$	
Parameter	**Ratio**	**90% CI**	**Ratio**	**90% CI**
R-warfarin	1.05	0.95–1.16	1.07	1.03–1.11
S-warfarin	1.09	0.97–1.23	1.10	1.03–1.18

Warfarin protein binding was unaffected by nebivolol. Similarly, nebivolol had no clinically significant effects on the anticoagulant activity of warfarin.

CONCLUSION: Once daily dosing of 10 mg nebivolol does not alter the single-dose PK or anticoagulant activity of warfarin.

PI-122

PROPOFOL ELIMINATION IN HUMAN BREAST MILK. M. J. Avram, PhD, M. Nitsun, MD, J. W. Szokol, MD, J. Saleh, MD, G. S. Murphy, MD, J. S. Vender, MD, K. Raikoff, MS, Northwestern University Feinberg School of Medicine, Evanston Northwestern Healthcare, Chicago, IL.

BACKGROUND/AIMS: Lactating women having operations under general anesthesia are advised to pump and discard their milk for 24 h after the procedure. We determined the kinetics of propofol elimination in breast milk to ascertain its safety after propofol administration.

METHODS: Three lactating women were studied after giving IRB-approved written informed consent. Patients were premedicated with midazolam 5 min before induction of anesthesia with fentanyl and propofol. Anesthesia was maintained with volatile anesthetics. Milk was collected using an electric breast pump before and at 5, 7, 9, 11, and 24 h after drug administration. Blood samples were collected before and at intervals up to 7 h after drug administration. Plasma and milk propofol concentrations were measured by HPLC with fluorescence detection. Using SAAM II, propofol elimination in breast milk was modelled simultaneously with plasma kinetics as the cumulative amount of drug in milk just as urinary elimination is modelled, but with a delay.

RESULTS: Plasma propofol kinetics were consistent with those reported by others. In 24 h, only 0.04 (± 0.04)% of the propofol dose was eliminated in milk, representing less than 0.05% of the propofol elimination clearance with a delay of nearly 6 h.

CONCLUSION: Consistent with the report of others for methohexital, meperidine, and diazepam, the amount of propofol eliminated in breast milk in the first 24 h after induction of anesthesia provides insufficient justification for interruption of breast feeding.