PII-107

NO PHARMACOKINETIC INTERACTION BETWEEN NEBIVOLOL AND FUROSEMIDE IN HEALTHY SUBJECTS. T. L. Morton, PhD, S. Liu, MS, J. L. Phillips, RN, C. M. Donnelly, MS, R. J. Rackley, PhD, Mylan Pharmaceuticals Inc., Morgantown, WV.

BACKGROUND: Potential interaction between nebivolol, a unique antihypertensive which couples vascular endothelial nitric oxide releasing capabilities with cardioselective β_1-blockade, and furosemide, was studied by comparison of pharmacokinetic (PK) parameter estimates in subjects genotyped for CYP2D6 status.

METHODS: Subjects [12 extensive (EM), 3 poor (PM) metabolizers] received 40 mg oral furosemide on Day 1. On Days 2–10, oral nebivolol (10 mg) was administered QD. On Day 11, nebivolol and furosemide were given QD. PK estimates for nebivolol and furosemide were assessed.

RESULTS: Co-administration of furosemide with nebivolol produced no statistically significant changes in PK estimates for *d,l*-nebivolol or its enantiomers in EM and PM subjects. The 90% confidence intervals for C_{max}, C_{SS} and AUC_τ in EM and PM subjects were within 80% - 125%. For furosemide, ANOVA testing of C_{max}, AUC_t, AUC_∞, and Cl/F revealed no interaction with nebivolol. The 90% confidence intervals for furosemide C_{max}, AUC_t and AUC_∞ were slightly different between treatments, but all passed through 100% and least squares mean ratios ranged from 0.93 to 0.95.

CONCLUSIONS: Regardless of CYP2D6 metabolizing status, there were no drug interactions observed that would affect the PK profile of either nebivolol or furosemide upon co-administration.

PII-108

IN VITRO LETROZOLE N-DEALKYLATION IS MAINLY CATALYZED BY HUMAN CYTOCHROME P450 (CYP) 3A. Z. Desta, PhD, B. A. Ward, BSc, D. A. Flockhart, MD, PhD, Division of Clinical Pharmacology, Indiana University School of Medicine, Indianapolis, IN.

BACKGROUND/AIMS: We used human liver microsomes (HLMs) to identify the CYP isoforms involved in letrozole metabolism. Letrozole, a potent inhibitor of aromatase (a rate-limiting enzyme in the biosynthesis of estrogens) is increasingly used to treat women with breast cancer. Although letrozole is cleared by metabolism via human hepatic CYPs, the specific enzymes involved have not been fully clarified, and as a result factors that influence it disposition and response are not known.

METHODS: Letrozole was incubated for 30 min at 37°C in human liver microsomes (HLMs, 0.5 mg protein/ml) and NADP-generating system with or without isoform specific inhibitors.

RESULTS: HPLC chromatograms of microsomal incubates of letrozole showed one major metabolite that was consistent with 4,4'-methanol-bisbenzonitrile (MI). The formation of MI in two HLMs (HG43 and HL091499) showed sigmoidal kinetics (apparent K_m, 38.3 and 38.4 μM; V_{max}, 8.8 and 20.0 pmol/min/mg protein; and Hill coefficients, 1.5 and 2.0 respectively). MI formation from letrozole (10 μM) correlated significantly with the activity of CYP3A. The IC50s for the inhibition of MI from letrozole (10μM) by ritonavir, troleandomycin, ketoconazole and pilocarpine were 0.3, 0.5, 0.4 and 25μM respectively.

CONCLUSION: Our data implicate CYP3A as a major catalyst of letrozole metabolism.

PII-109

ASSESSMENT OF ETHNIC DIFFERENCES IN THE PHARMACOKINETICS OF VALSARTAN. G. Sunkara, PhD, C. Thang-Dittman, PharmD, C. Yeh, PhD, M. Ligueros-Saylan, MD, P. Prasad, PhD, N. Masuda, N. Koseki, Y. Fukui, Novartis Pharmaceuticals, East Hanover, NJ.

PURPOSE: To assess the ethnic differences in the pharmacokinetics and pharmacodynamics of valsartan between Japanese and Caucasian subjects.

METHODS: In this open label, parallel design study, a total of 15 healthy male Japanese and 15 healthy male Caucasian subjects received a single oral dose of 160 mg valsartan (Diovan®) capsule. Blood samples were collected at pre-determined time intervals to assess plasma valsartan, plasma renin activity, plasma aldosterone and plasma angiotensin II.

RESULTS: Demographic data were similar between Japanese and Caucasian subjects. The time (Tmax) to reach peak plasma concentrations of valsartan was in the range of 1 - 6 h. The mean (±SD) Cmax of valsartan was comparable (p-value = 0.217) between Japanese and Caucasian subjects (3.3 (±1.97) vs. 3.5 (±0.84) μg.h/mL). Similarly, the mean (±SD) plasma exposure indicated by $AUC_{0-\infty}$ (23 (±9.4) vs. 23.8 (±5.6) μg.h/mL) was also comparable (p-value =0.450). The mean (±SD) elimination half-life ($t_{1/2}$) of valsartan was 7.7 (±1.5) h and 9.6 (±4.8) h in Japanese and Caucasian subjects, respectively. No significant difference (p-value>0.1) was found between two ethnic groups for plasma rennin activity, angiotensin II and aldosterone at 2, 4, and 8 hours post dose.

CONCLUSIONS: Pharmacokinetics of valsartan were similar between healthy male Caucasian and Japanese subjects.

PII-110

COMPARTMENTAL ANALYSIS OF SAQUINAVIR (SQV) PHARMACOKINETICS (PK). J. Z. Zack, A. Forrest, O. O. Okusanya, S. Rosenkranz, M. F. Para, E. Adams, K. Yaresheski, R. C. Reichman, G. D. Morse, SUNY-UB, Harvard University, Ohio State University, NIAID, Washington University, University of Rochester, Buffalo, NY.

AIMS: SQV is a PI used, in combinations, in patients with HIV. Because compartmental PK analyses are unavailable, to date, our aim is to develop & report a valid PK model & parameters for SQV.

METHODS: Ten healthy HIV seronegative subjects were administered SQV 1600 mg PO q12h for 7 days (co-administered with amprenavir 600 mg PO q12h for 10 days for & efavirenz 600 mg q24h for 14days) as a part of AACTG A5043. Blood samples were obtained pre-dose, at 0, 1, 2, 3, 4, 5, 6, 8, 10 & 12h post-dose. Samples were analyzed for SQV (LCMSMS) & fit to candidate models (ADAPT II). Data were weighted by the estimated inverse measurement variance & model discrimination was by Akaike's Information Criterion.

RESULTS: SQV PK was best described by a linear two compartment model with: 1st order absorption (ka) following a lag time (TLag), central (Vc) & peripheral (Vp) volumes, distributional (CLd) & total (CLt) clearances. Mean (CV) parameter values were: Vc 0.595L/kg (0.67), Vp 7.95L/kg (0.53), CLd 1.57L/h/kg (0.39), CLt 6.35L/h/kg (0.27), & terminal half-life 9.82h (0.62). The goodness of fit was excellent with a median r^2 of 0.997 (range 0.90–1).

CONCLUSIONS: This compartmental model for SQV PK will enable simulations, designs of studies, MAP Bayesian estimators & PK/PD individualization.