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PHARMACOKINETIC DISPOSITION OF NEBIVOLOL IN EXTENSIVE AND POOR CYP2D6 METABOLIZERS. A. A. Shaw, PhD, J. Ziemniak, PhD, S. Liu, MS, S. W. Chervenick, PhD, R. J. Rackley, PhD, Mylan Pharmaceuticals Inc, Gwynedd Pharmaceuticals, Morgantown, WV.

BACKGROUND: Nebivolol (N) is considered to be a unique cardiovascular agent studied worldwide for the treatment of hypertension, CHF and other cardiovascular conditions owing to vascular endothelial nitric oxide stimulating capabilities and its highly selective β_1-antagonism. It is directly glucuronidated to a set of active metabolites believed to make a clinically important contribution to therapy. It is also metabolized by polymorphic CYP2D6 to active hydroxy-moeities, which are further glucuronidated. The present study examined the steady-state kinetics of N in extensive (EM) and poor (PM) CYP2D6 metabolizers.

METHODS: Twenty-two healthy adult subjects completed (16 EMs and 6 PMs). N (10 mg) was administered once daily for 14 days, with steady-state assessments on Days 12 thru 14 and PK profiling on Day 14 for N and nebivolol glucuronides (G-UD).

RESULTS: N was well tolerated by both groups.

	EM		PM	
Parameter	**N**	**G-UD**	**N**	**G-UD**
AUC (ng hr/mL)	19.73	433.2	633.2	2804
C_{max} (ng/mL)	3.45	52.76	32.11	220.5
T_{max} (hr)	1.19	2.69	3.67	3.67
$t_{1/2}$ (hr)	12.66	7.43	56.05	32.81
CI/F (L/hr)	657.4	44.31	16.32	3.89

CONCLUSIONS: Despite the PK differences between EMs and PMs, clinical trials have established that there are no clinical efficacy or safety differences between the two groups.

PII-100

HERBAL COMPONETS INHIBIT P-GP MEDIATED DIGOXIN TRANSPORT IN TRANSWELL CULTURED CACO-2 CELL MODEL. N. He, PhD, X. Collins, Y. Huang, T. Edeki, MD, PhD, Morehouse School of Medicine, Morehouse College, Atlanta, GA.

BACKGROUND/AIMS: There is an increased attention towards herbal supplement induced drug-drug interactions. Five herbal components from ginseng and ginkgo biloba were investigated for their inhibitory effects on P-gp mediated digoxin transport.

METHODS: The 12 wells Transwell Plate with growing Caco-2 cell on inserts were used, and [^{3}H]-digoxin was used as the substrate drug. The [^{3}H]-digoxin transport crossing the Caco-2 cell monolayer in the presence and absence of herbal ingredients was measured. Then, the [^{3}H]-digoxin Net Transport and the transport normalized to control were calculated.

RESULTS: At the 100 μM herb level, the Net Transports in samples treated with ginsenoside R_e, R_{b1}, R_{b2}, and quercetin were 6887.67, 7010.33, 7175.00, and 2852.00 (CPM values, mean $\pm$ SD), respectively; and the normalized transports were 75.0%, 78.7%, 80.5%, and 32.0%, respectively. However, samples treated with ginsenoside R_d showed no difference from blank control (methanol, solvent for reagents) (8307.66, 93.2%). The P-gp inhibitor of ketoconazole (40 μM) was set up as positive control, and the related values were 1073.30 and 12%, respectively.

CONCLUSIONS: Our findings suggest that ginsenoside R_e, R_{b1}, R_{b2}, and quercetin are capable of inhibiting P-gp mediated digoxing transport at 100 μM in Transwell cultured Caco-2 cell model. It may result in adverse drug interactions when co-administered with P-gp substrate drugs in vivo. Further studies are required to elucidate the molecule mechanism of these effects.

PII-101

PHARMACOKINETICS OF NEBIVOLOL AND RAMIPRIL ARE NOT AFFECTED BY CO-ADMINISTRATION. 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: The unique antihypertensive action of nebivolol (N) is believed to be due to combined β_1-receptor antagonism and endothelial nitric oxide releasing capabilities which have been reported to improve hemodynamics and left ventricular function. ACE inhibitors are often used with β-blockers in cardiovascular therapy. Thus, co-administration of N and ramipril (R) was assessed for pharmacokinetic (PK) interaction.

METHODS: Healthy subjects [12 extensive (EM), 3 poor (PM) metabolizers, from CYP2D6 genotype] in this open-label, randomized, two parallel group study received oral N (10 mg QD) or R (5 mg QD) on Days 1–10 or 21–30. On Days 11–20, oral R plus N were given. Blood was taken on Days 10, 20, 30 and prior to the 8th and 9th doses of each phase. Plasma *d*- and *l*-N and/or R and ramiprilat (Rlat) levels were measured by LC/MS. PK parameter estimates were statistically compared using 90% confidence intervals (CIs).

RESULTS:

	C_{peak}		AUC_t	
Analyte	**Ratio**	**90%CI**	**Ratio**	**90%CI**
EM-*d,l*-N (n = 12)	0.96	0.78–1.18	0.97	0.92–1.02
PM-*d,l*-N (n = 3)	0.90	0.75–1.07	0.93	0.87–1.00
Rlat (n = 15)	1.03	0.98–1.09	1.02	0.99–1.05

No clinically relevant changes in the PK of *d*-N or *l*-N enantiomers were noted and R data were at the assay's LOQ.

CONCLUSION: Co-administration of N and R did not appear to affect the clinical PK profile of either antihypertensive agent.

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POPULATION PHARMACOKINETIC (PPK) ANALYSIS OF PEGYLATED INTERFERON ALFA-2B (PEG-INTRON) IN PATIENTS WITH CHRONIC MYELOGENOUS LEUKEMIA (CML). S. Gupta, PhD, D. Cutler, MD, J. Jen, PhD, K. Kolz, R. White, PhD, Schering-Plough Res. Inst., Kenilworth, NJ.

PURPOSES: To assess PPK of PEG-Intron in CML patients. This was a randomized, multicenter, open-label, parallel group, Phase III trial of safety and efficacy of PEG Intron vs Intron A in adult subjects with newly diagnosed chronic-phase CML.

METHODS: Nonlinear mixed-effects modeling was used to analyze the sparsely sampled concentration data from a clinical efficacy trial. PEG-Intron 3–6 μg/kg was administered subcutaneously once a week, and blood samples were collected up to 48 weeks of treatment. A total of 624 samples collected from 137 patients were included in the analysis. Covariates in the analysis included weight, sex, age, race, concomitant medication, serum creatinine, and estimated creatinine clearance (CLcr).

RESULTS: The clearance at treatment week 4 was 42.3 L/day (patients with CLcr 120 ml/min) with interpatient variability 30%. At treatment week 48, the clearance value was reduced to 69% of its week 4 level. CLcr had a statistically significant influence on the clearance of PEG-Intron. The clearance of PEG-Intron in patients with CML was 40% higher than that of hepatitis C virus infected patients.

CONCLUSIONS: The dose of PEG-Intron 6.0 μg/kg/week appeared appropriate in the treatment of patients with CML.