## PI-152

DISPOSITION OF DESLORATADINE IN HEALTHY VOLUNTEERS. L. Reyderman, PhD, R. Ramanathan, PhD, S. Chowdhury, PhD, K. Alton, MS, P. Statkevich, PhD, M. Wirth, PhD, Schering-Plough Research Institute, Kenilworth, NJ.

**BACKGROUND:** Desloratadine (DL), a major active metabolite of loratadine (LOR), is a long-acting tricyclic antihistamine with selective peripheral histamine H1-receptor antagonist activity. The objective of this study was to characterize the absorption, metabolism and excretion of DL following oral capsule administration.

**METHODS:** Six healthy male volunteers (ages 18–40 years) received a single 10mg (100μCi) $^{14}$C-DL dose in a Phase 1, open-label study. Blood, urine and feces were collected over 240 hr.

**RESULTS:** DL was well absorbed. With the exception of a single subject, DL was extensively metabolized; major pathway consisted of hydroxylation and subsequent glucuronidation. 3OH-DL-glucuronide was identified as a primary plasma metabolite (47% of circulating plasma $^{14}$C). Drug-derived radioactivity was excreted in both urine (41%) and feces (47%). One subject, identified as a poor metabolizer, exhibited 10-fold greater exposure to DL and correspondingly lower amounts of 3OH-DL in plasma and excreta. Disposition of DL in this subject was characterized by slow absorption, slow metabolism and prolonged elimination ($t_{1/2}$=110 hr vs. mean $t_{1/2}$=19.5 hr, n=5). All metabolites detected following DL administration were characterized following an oral LOR dose.

**CONCLUSIONS:** Characterization of metabolite and excretion profile of orally administered DL identified a phenotypic polymorphism of DL metabolism. Further clinical studies confirmed lack of safety concern associated with this phenomenon.

## PI-153

EFFECT OF GINKGO ON CYP2C9: IN VITRO AND IN VIVO STUDIES. D. J. Greenblatt, MD, L. L. von Moltke, MD, E. S. Perloff, PhD, Y. Luo, J. S. Harmatz, BA, E. Bedir, PhD, I. A. Khan, PhD, P. Goldman, MD, Tufts University School of Medicine, University of Mississippi, Harvard Medical School, Boston, MA.

**PURPOSES:** In vitro and clinical studies evaluated the effect of exposure to Ginkgo biloba (GB), or its components, on the activity of human CYP2C9.

**METHODS:** 29 chemical constituents of GB were isolated, purified (J Agr Food Chem 2002; 50:3150), and tested as inhibitors of human CYP2C9 in vitro, based on flurbiprofen (F) hydroxylation activity in human liver microsomes (J Pharm Pharmacol 2004; 56: 1039). Healthy volunteers (n=11) received 100 mg of F on two occasions in a crossover study, preceded by two 120-mg doses of GB or of matching placebo (P).

**RESULTS:** CYP2C9 inhibition in vitro was produced by amentoflavone (IC50=0.035 μM), sesamin (21.2 μM), quercetin (25.8 μM), and 3-nonadec-8-enyl-benzene-1,2-diol (5.6 μM). Ginkgolides, bilobalide, and flavonol aglycones had weak or negligible inhibitory activity. Mean (±SE) clinical kinetic parameters for F when given with P and GB, respectively, were: peak plasma concentration, 12.2±1.0 vs. 11.6±0.8 μg/ml; elimination half-life, 4.3±0.5 vs. 4.0±0.6 hr; clearance, 31±4 vs. 29±3 ml/min. Differences were not significant.

**CONCLUSIONS:** Several components of GB_especially amentoflavone_are potentially important inhibitors of CYP2C9. However coadministration of F (an index substrate for CYP2C9) with usual doses of GB in humans had no effect on the kinetics of F. Potential CYP2C9 inhibitors in GB either are not present in sufficient quantities to produce clinically detectable inhibition in vivo, or do not reach the liver at inhibitory concentrations.

## PI-154

POPULATION PHARMACOKINETIC MODEL OF SEDATIVE DOSES OF GPI15715 AND PROPOFOL LIBERATED FROM GPI15715. E. Gibiansky, PhD, L. Gibiansky, PhD, J. Enriquez, MD, Guilford Pharmaceuticals Inc., Metrum Research Group, Baltimore, MD.

**BACKGROUND:** GPI15715 (AQUAVAN® Injection, AQ) is a water soluble prodrug of propofol (PR). Pharmacokinetics (PK) of PR liberated from AQ differ from those of PR lipid emulsions. We developed a population PK model of AQ and liberated PR and identified covariates that influenced their PK.

**METHODS:** In a Phase II colonoscopy sedation study, 5 minutes after fentanyl citrate iv dose (11–201 μg) patients received an AQ iv bolus and up to 4 supplemental iv doses (total dose 495–1675 mg). A total of 597 AQ and 599 PR concentrations from 69 males and 89 females were analyzed using NONMEM. Covariates included age (20–85 yrs, 18 patients ≥ 65 yrs), weight (WT 45–140 kg), lean body weight (LBW 37–81 kg), BMI, gender, fentanyl citrate exposure, albumin, creatinine clearance, and lab values.

**RESULTS:** Linear 2-comparment models for AQ and PR with a delay compartment between them described the data. $CL^{AQ}$, $V_1^{AQ}$ and $CL^{PR}$, $V_1^{PR}$ increased proportionally with LBW. Model parameters (%SE) under assumption of 100% AQ metabolism to PR were: $CL^{AQ}$=0.27 L/min (21%), $V_1^{AQ}$=6.4 L (6%), $K_{12}^{AQ}$=0.023 1/min (56%), $K_{21}^{AQ}$=0.0032 1/min (52%), $K^{AQ\text{-}PR}$=0.41 1/min (12%), $V_1^{PR}$=1 L (fixed), $CL^{PR}$=3.7 L/min (18%), $K_{12}^{PR}$=3.8 1/min (25%), $K_{21}^{PR}$=0.03 1/min (27%), $CL^{AQ}_{LBW}$=2.5 %/kg (12%), $V_1^{AQ}_{LBW}$=1.8 %/kg (21%), $CL^{PR}_{LBW}$=$V_1^{PR}_{LBW}$=1.6 %/kg (27%).

**CONCLUSIONS:** Linear population PK model adequately described the data. LBW was a better predictor than WT. Fentanyl citrate did not affect the PK. No clinically significant influence of age was detected.

## PI-155

PHARMACOKINETIC PROFILE OF PARECOXIB SODIUM, AN INJECTABLE PRODRUG OF THE COX-2-SELECTIVE INHIBITOR, VALDECOXIB. S. Krishnaswami, PhD, Pfizer, Ann Arbor, MI.

**BACKGROUND:** Parecoxib sodium is an injectable prodrug of the Cox-2 inhibitor, valdecoxib in regulatory review in the US for the management of acute pain.

**AIM:** To compare the pharmacokinetic (PK) profiles of valdecoxib after administration of IV and IM parecoxib sodium relative to valdecoxib (BEXTRA®) tablets.

**METHODS:** PK data were obtained from a study comparing single and multiple 5, 10, and 20 mg doses of oral valdecoxib tablet and IV parecoxib sodium solution (n=36), and a study comparing 20 mg IM and IV parecoxib sodium solution (n=16) in healthy volunteers.

**RESULTS:** The 90% CIs for oral/IV treatment ratios of valdecoxib AUC after adjusting for molecular weight difference between parecoxib and valdecoxib were within 84–118% across single and multiple doses of 5, 10 and 20 mg. IM and IV parecoxib sodium were bioequivalent for valdecoxib AUC and Cmax. Valdecoxib Cmax was observed around 0.5, 0.8 and 2.3 hours after IV and IM parecoxib sodium and oral valdecoxib tablets, respectively, with mean oral/IV ratios within 0.51–0.78 due to the rapid conversion of parecoxib sodium (t1/2~22 min) to valdecoxib. Valdecoxib T1/2 (~8 hours) was unaffected by route of administration.

**CONCLUSIONS:** The pharmacokinetic profile of valdecoxib is similar when administered orally as valdecoxib tablets or as IM/IV parecoxib sodium, indicating no PK limitations to transitioning from parenteral to oral treatment.