PII-118

MECHANISM-BASED INHIBITION OF CYP3A4 AND CYP3A5 BY SEVEN INHIBITORS. K. C. Patki, L. L. von Moltke, MD, D. J. Greenblatt, MD, Tufts University School of Medicine, Boston, MA.

We evaluated the potential for inhibition of CYP3A4 and CYP3A5 using seven mechanism-based inhibitors: troleandomycin (TAO), erythromycin (ERY), 6′, 7′-dihydroxybergamottin (DHB), diltiazem (DIL), verapamil (VER), ethynyl estradiol (EE) and ritonavir. These inhibitors were preincubated with NADPH and recombinant enzymes (CYP3A4 and CYP3A5) for 20 minutes. Enzyme activity was determined by 1-hydroxy triazolam (1-OH TRZ) formation from triazolam (250μM). Using recombinant enzymes, IC50 values were reduced by preincubation with inhibitors. IC50 values with preincubation with CYP3A4 using TAO, ERY, DHB, DIL, VER, EE and ritonavir were: 1.7, 2.9, 0.9, 7, 3.3, 4.4 and 0.06 μM respectively. With CYP3A5, IC50 values with preincubation were: 44.5, 77.5, 1.2, 21.8, 8, 17 and 0.1 μM respectively. The pattern of 1-OH TRZ IC50 values suggested two classes of mechanism-based inhibitors, with nonmacrolides showing less than a 4-fold difference between CYP3A4 and CYP3A5, and macrolides showing more than a 25-fold difference. Individuals polymorphically expressing CYP3A5 in significant amounts may have greater susceptibility to interactions involving nonmacrolide mechanism-based inhibitors than that seen with reversible inhibitors. However, macrolide mechanism-based inhibitors may be less susceptible to interactions in these subjects.

PII-119

TRADITIONAL AQUEOUS KAVA EXTRACTS INHIBIT CYP4501A2 IN HUMANS. S. Russmann, MD, Y. Barguil, M. Wenk, R. Theurillat, P. Cabalion, E. Choblet, K. Rentsch, B. H. Lauterburg, University of Bern, Bern, Switzerland.

Purpose: Consumption of traditional aqueous kava (Piper methysticum Forst. f.) extracts is common in the Pacific region, whereas commercial products have been withdrawn in many countries due to rare but severe hepatotoxicity. Previous in-vitro studies suggest that kavalactones are metabolized via CYP450 and that they have an inhibitory effect on these enzymes, which may be relevant for interactions as well as for the mechanism by which kava rarely causes hepatotoxicity. **Methods:** In a cross-over study, 6 healthy chronic kava consumers from New Caledonia (estimated intake of kavalactones 7-27 grams per week for >6 years) received probe-drug cocktails on two consecutive days. After complete stop of kava drinking for 4 weeks they received the same probe-drugs again. Phenotypic trait measurements were determined for the metabolizing CYP450 enzymes at both time points. **Results:** Serum concentration ratios with and without kava exposure for paraxanthine/caffeine (CYP1A2) were 0.3±0.1 vs. 0.6±0.2 (mean±SD, p=0.02), for 1-OH-midazolam/midazolam (CYP3A4) 0.4±0.1 vs. 0.4±0.2 (p=0.75), and for 6-OH-chlorzoxazone/chlorzoxazone (CYP2E1) 0.9±0.6 vs. 1.4±1.1 (p=0.16). Urinary recovery ratios for debrisoquine/OH-debrisoquine (CYP2D6) were 0.8±0.4 vs. 0.8±0.6 (p=0.82) and for mephenytoin/4-OH-mephenytoin (CYP2C19) 2.0±0.9 vs. 1.5±0.6 (p=0.29). **Conclusion:** Traditional kava drinking in high amounts inhibits CYP1A2, but does not affect CYP2D6, CYP2C19, CYP2E1 or CYP3A4 activities.

PII-120

A POPULATION PHARMACOKINETIC MODEL FOR PENCICLOVIR IN HUMAN EYE AND PLASMA. F. Schenkel, E. Baglivo, MD, M. Gex-Fabry, Y. Daali, PharmD, M. Kondo Ostreicher, MD, P. Dayer, Prof, Geneva University Hospitals, Geneva, Switzerland.

Penciclovir, the metabolite of famciclovir, is a nucleoside analogue active against varicella zoster and herpes simplex type I, II and Ebstein-Barr virus.

OBJECTIVE: Evaluate the pharmacokinetics of penciclovir in human aqueous humour and plasma after oral administration of famciclovir by means of a population pharmacokinetic approach. **METHOD AND ANALYSIS:** 31 patients undergoing cataract surgery received 500mg famciclovir at various times before surgery. The concentrations of penciclovir in both blood and aqueous humour were assayed by high-performance liquid chromatography with fluorescence detection. Population pharmacokinetic software NONMEM was used to calculate pharmacokinetic parameters in the eye and plasma. **RESULTS:** A two compartment model adequately described the penciclovir pharmacokinetics. Population and individual pharmacokinetic parameters were determined for plasma and aqueous humour. At 2, 4 and 6 hours, the ratios of the predicted concentrations in aqueous to the concentrations in plasma were 14%, 28% and 39%, respectively. The mean elimination half-live from plasma and aqueous humour were 3.04 hours and 1.98 hours, respectively, with 26% interindividual variability. In aqueous humour, the predicted Cmax and Tmax were 0.72 mg/ml and 3.58 hours, respectively. **CONCLUSION:** The selected population pharmacokinetic model accurately characterised penciclovir pharmacokinetics in both aqueous humour and plasma and allowed to calculate pharmacokinetic parameters.

PII-121

AN OPEN LABEL BIOEQUIVALENCE STUDY OF ORAL SAQUINAVIR (RO 31-8959) USING A STABLE ISOTOPE FORMULATION OF SAQUINAVIR AS AN "IN VIVO" INTERNAL STANDARD. T. Peluso, MBBS, DCPSA, T. G. Mant, BSc, FRCP, FFPM, D. M. Amin, MRCGP, DCPSA, G. R. McClelland, PhD, MIBiol, Guy's Drug Research Unit, Quintiles Limited, Roche Products Limited, London, United Kingdom (Great Britain).

This study was designed to compare the relative bioavailabilities of two different formulations of the HIV protease inhibitor, saquinavir.

In view of the high intra-subject variability associated with saquinavir a stable isotope was employed. We predicted a reduction in intra-subject variability of 40–60% consequently allowing fewer healthy volunteers to be exposed to the trial drug. Bioequivalence testing was performed using the relative AUC (RAUC) and the relative Cmax (RCmax); the ratio of AUC (or Cmax) from the unlabelled capsule dose to the AUC (or Cmax) from the concurrent labelled dose. We expected that the relative pharmacokinetic measures would have a smaller variance than the untransformed pharmacokinetic measures. For RAUC and RCmax bioequivalence was established according to the equivalence criteria (80-125%). Bioequivalence was also established based on the unlabelled parameters for AUC and Cmax according to the equivalence criteria (80-125%). The estimate of within subject variability (CV) for RAUC was reduced compared to the unlabelled AUC data (27.78% versus 33.74%). On the contrary, the estimate of within subject variability (%CV) for RCmax was higher than for the unlabelled Cmax data (38.32% versus 33.94%). These results indicated that the use of the relative parameter had little impact on the intra-subject variability contrary to what was predicted.