PI-121

RENAL FUNCTION AND ALBUMIN CONCENTRATION ARE DETERMINANTS OF MYCOPHENOLIC ACID PHARMACOKINETICS. R. M. van Hest, PharmD, T. van Gelder, MD, PhD, A. G. Vulto, PharmD, PhD, R. A. Mathot, PharmD, PhD, Erasmus University Medical Center Rotterdam, Rotterdam, Netherlands.

PURPOSE Mycophenolic acid (MPA) is an immunosuppressant used in renal transplantation. The compound exhibits considerable inter-patient pharmacokinetic variability. In this study a population pharmacokinetic model was developed for MPA to assess the relationship between MPA clearance (Cl) and both renal function and albumin concentrations.

METHODS Data were obtained from a randomised concentration controlled trial, in which 140 patients participated and individual pharmacokinetics were assessed on 9 occasions during a 24 week period.

RESULTS A total of 6523 plasma concentration-time data were simultaneously fitted to a two compartment model with time-lagged first order absorption using non-linear mixed effects modelling (NONMEM). Creatinine clearance (CrCl) significantly correlated with MPA Cl ($p<0.001$). An CrCl increase from 10 to 30 mL/min resulted in a decrease in MPA Cl from 50 L/h to 41 L/h. A further increase to 100 mL/min yielded a Cl of 33 L/h. MPA Cl correlated ($p<0.001$) with plasma albumin (ALB) as well; an ALB fall from 50 to 30 g/L corresponded with a Cl rise from 19 to 38 L/h.

CONCLUSION Impaired renal function was associated with an increased Cl of MPA, especially with CrCl levels below 30 mL/min. This may be explained by an increase of the unbound fraction. The latter is corroborated by the fact that Cl increases with decreasing plasma albumin concentration. Following renal transplantation changes in graft function and albumin concentration affect MPA disposition and thereby its pharmacodynamics.

PI-122

ASSESSMENT OF BILIARY EXCRETION IN HUMANS USING A NOVEL OROENTERIC TUBE. B. M. Johnson, PhD, G. Ghibellini, MS, W. D. Heizer, MD, K. L. Brouwer, PharmD, PhD, University of North Carolina at Chapel Hill, Chapel Hill, NC.

The biliary tract is an important route of elimination and potential site of toxicity for many xenobiotics. Quantification of biliary excretion in healthy volunteers is logistically challenging and is rarely defined during drug development. The current study uses a novel oroenteric tube to examine the pharmacokinetics of mebrofenin, a compound that undergoes rapid hepatic uptake and extensive biliary excretion. A custom-made multi-lumen oroenteric tube was positioned in the duodenum of four healthy volunteers (3 male, 1 female), subjects were positioned under a gamma camera and 2.5 mCi of ^{99m}Tc-mebrofenin was administered intravenously. Duodenal aspirates, blood samples, and urine were collected periodically for 3 h. Sincalide (cholecystokinin-8) was administered intravenously 2 h after mebrofenin to stimulate contraction of the gallbladder, and gamma scintigraphy was used to determine gallbladder ejection fraction. Total body clearance of mebrofenin approximated liver blood flow, and the oroenteric tube efficiently recovered the majority of excreted bile and mebrofenin. When corrected for gallbladder ejection fraction, 77-101% of the dose was recovered. This novel oroenteric tube and clinical protocol provide a useful method to quantify biliary excretion in healthy volunteers.

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	Subject			
	1	2	3	4
Ejection fraction	0.86	0.82	0.12	0.86
Dose collected in bile (%)	84	66	35	84
Clearance (ml/min/kg)	16.58	17.02	19.88	17.33
Biliary clearance (ml/min/kg)	15.02	11.47	7.81	15.61

PI-123

ABSENCE OF CIRCADIAN VARIATION IN THE PHARMACOKINETICS (PK) OF LOPINAVIR/RITONAVIR (LPV/R) IN A ONCE-DAILY (QD) DOSING REGIMEN IN HIV-1-INFECTED SUBJECTS. R. van Heeswijk, PharmD, PhD, M. Bourbeau, BSc, I. Seguin, RN, D. Cote, RN, P. Giguere, BPharm, G. Garber, MD, B. Cameron, MD, The Ottawa Hospital, The Ottawa Health Research Institute, Ottawa, Canada.

Background Previous studies suggest a circadian phase dependency in the PK of protease inhibitors. This may have practical implications, especially for qd regimens. This study explored the PK of LPV/r 800/200 mg qd after am versus pm dosing.

Methods A randomized two-way cross-over study in HIV+ subjects taking LPV/r bid + 2 NRTIs. 24h PK were assessed after 2 weeks of LPV/r qd at 8 am and 7 pm, resp. LPV/r was taken with a standardized meal (800 kCal, 30% from fat) after fasting for 5 h. LPV/r concentrations were measured by LC/MS/MS. PK were analyzed by noncompartmental methods.

Results 12 subjects completed the study (all men, mean age/weight 44 yrs/80 kg). The median (IQR) LPV AUC24h, Cmax and C24h after am and pm dosing was 143 (100-235) h*mg/L, 12.8 (8.8-19.6) mg/L, 1.2 (0.6-2.4) mg/L, and 171 (122-230) h* mg/L, 12.9 (8.4-16.9) mg/L, 1.0 (0.4-1.7) mg/L, resp. The intra- and inter-subject variability in the LPV AUC24h was 19 and 39%, resp. The geometric mean ratio (GMR, am/pm) and 90% CI of the LPV AUC24h, Cmax, and C24h was 0.91 (0.78-1.05), 1.09 (0.99-1.21), and 1.24 (0.78-1.97), resp. For 11/12 subjects RTV concentrations remained below 2.1 mg/L. The GMR (90% CI) of the RTV AUC24h, Cmax, and C24h was 0.94 (0.81-1.11), 1.35 (1.09-1.68), and 1.04 (0.7-1.54), resp.

Conclusion No clinically relevant differences were observed in the PK of LPV/r after am or pm dosing with food. This suggests that LPV/r qd can be taken in the morning or evening, which may facilitate adherence.

PI-124

ASSESSMENT OF BOTANICAL SUPPLEMENTATION ON HUMAN CYTOCHROME P450 PHENOTYPE: CITRUS AURANTIUM, ECHINACEA, MILK THISTLE, SAW PALMETTO. B. J. Gurley, PhD, S. F. Gardner, PharmD, M. A. Hubbard, MS, K. Williams, PhD, B. Gentry, MD, J. Carrier, PhD, D. Edwards, PhD, I. Khan, PhD, UAMS, College of Pharmacy, UAMS, College of Medicine, University of Arkansas, Fayetteville, Wayne State University, University of Mississippi, Little Rock, AR.

Objectives: Phytochemical-mediated modulation of cytochrome P-450 activity may underlie many herb-drug interactions. Single time-point, phenotypic metabolic ratios were used to determine if supplementation with citrus aurantium, echinacea, milk thistle, or saw palmetto affected CYP1A2, CYP2D6, CYP2E1, or CYP3A4 activity.

Methods: Twelve healthy volunteers were randomly assigned to receive each supplement for 28 days. A 30-day washout period was interposed between each supplementation phase. Probe drug cocktails of midazolam, caffeine, chlorzoxazone, and debrisoquine were administered before and at the end of each supplementation period. Pre- and post-supplementation phenotypic trait measurements were determined for CYP3A4, CYP1A2, CYP2E1, and CYP2D6 using 1-hydroxymidazolam/midazolam serum ratios (1-hour), paraxanthine/caffeine serum ratios (6-hour), 6-hydroxychlorzoxazone/chlorzoxazone serum ratios (2-hour), and debrisoquine urinary recovery ratios (8-hour collection), respectively. Phytochemical content was determined for each supplement.

Results: Comparisons of pre- and post-supplementation phenotypic ratios indicated that these particular supplements had no significant effect on CYP activity. Citrus aurantium was devoid of the CYP3A4 inhibitor, 6,7-dihydroxybergamottin.

Conclusions: Botanical supplements containing citrus aurantium, echinacea, milk thistle, or saw palmetto appear to pose a minimal risk for CYP-mediated herb-drug interactions in humans.