PI-106

POPULATION PHARMACOKINETICS (PopPK) OF VALPROIC ACID (VPA) FOLLOWING RAPID INFUSION IN EPILEPSY PATIENTS. S. Dutta, PhD, J. C. Cloyd, PharmD, Abbott Laboratories, University of Minnesota, Abbott Park, IL.

Purpose: Characterize VPA PopPK following rapid infusion. **Methods:** Epilepsy patients (N=112), with or without enzyme inducing comedications, were randomized to either 3.0 or 1.5 mg/kg/min 5-min VPA infusions. VPA plasma albumin binding was examined using 1 & 2 binding-site models. PopPK analysis of total & free plasma VPA concentrations (up to 6 h post-infusion) was performed using NONMEM. Effect of enzyme-induction on clearance (CL) and cholesterol, creatinine, age & inductions status on primary protein binding (PB) constant (K1) was examined using the chi-square test. **Results:** One & 2-comparment models optimally characterized total & free VPA concentrations, respectively. Estimated parameters±SE for uninduced subjects were: totalCL=1.21±0.0854 L/h, totalV=12.3±0.373 L, freeCL=18.4±8.17 L/h, freeV1=2.09±2.43 L, freeQ=63.7±61.7 L/h, & freeV2=65.8±25.7 L. Enzyme-induction was a significant covariate; totalCL & freeCL increased by 61 & 24%. VPA PB was nonlinear; 2-site PB model parameters±SE, viz., N1, K1, N2, & K2, were 1.54±0.108, 11.9±1.99 (1/mM), 0.194±0.0783, and 164±141 (1/mM). No significant covariates were identified for VPA PB. Inter-subject variabilities in totalCL, freeCL, & K1 were 45, 75 & 30%. **Conclusions:** These PopPK models accounting for induction status and albumin levels may be used to predict VPA concentrations. Accounting for other factors such as health status and genetics may reduce some of the unexplained variability and improve model predictability.

PI-107

ORAL CLOTRIMAZOLE (CLZ) DECREASES PRESYSTEMIC METABOLISM OF CYTOCHROME P450 (CYP) 3A4 SUBSTRATES. S. S. Shord, PharmD, L. Chan, PharmD, J. R. Camp, BSc, E. Vasquez, PharmD, C. Baum, MD, R. E. Molokie, MD, University of Illinois at Chicago, Chicago, IL.

Although human hepatocytes usually provide an accurate estimate of drug metabolism in vivo, oral CLZ appears to induce CYP3A4 in vitro and inhibit CYP3A4 in vivo. This discrepancy indicates that predicting the effect of a drug on CYP activity in vivo from hepatocytes may be limited. Therefore, we investigated the effects of oral CLZ on CYP3A4 activity using midazolam (MDZ) as a specific probe. Ten healthy volunteers randomly received oral CLZ 10mg 3 times daily x 5 days or no treatment (C) before their study visit. The study included 2 inpatient (oral MDZ 2mg) and 2 outpatient visits (IV MDZ 0.025 mg/kg) with the visits separated by 2 weeks. Blood samples were drawn at the following times: 0, 0.5, 1, 2, 4, 5, 6, 12 and 24 h after oral MDZ and 0, 0.25, 0.5, 1, 2, 4, 5, 6 h after IV MDZ. The plasma concentrations for MDZ were quantified using high performance liquid chromatography and were fitted to a non-compartmental model. The maximal plasma concentration (CLZ 18±7.8 vs. C 12±4.7 ng/ml; $p<0.025$) and area under the curve (CLZ 55±12 vs. C 42±14 ng*h/ml; $p=0.040$) for oral MDZ increased after receiving CLZ. In contrast, CLZ did not affect the pharmacokinetic parameters for IV MDZ. The plasma concentrations of CLZ and 1-hydroxyMDZ will be determined, as well. In summary, CLZ increases the systemic absorption of orally administered CYP3A4 substrates, but does not affect the systemic clearance of IV administered CYP3A4 substrates.

PI-108

CELECOXIB PHARMACOKINETICS IN PEDIATRIC CANCER PATIENTS – THE EFFECTS OF FOOD AND PHARMACOGENETICS. D. C. Stempak, MSc, B. L. Bukaveckas, PhD, M. W. Linder, PhD, G. Koren, MD, S. Baruchel, MD, Hospital for Sick Children, University of Louisville, Toronto, Canada.

PURPOSE: To determine the single dose and steady state (SS) pharmacokinetics (PK) of the selective COX-2 inhibitor celecoxib in pediatric cancer patients (with & without food) and to correlate PK and CYP2C9 genotype.

METHODS: Celecoxib (250mg/m^2) was administered to the patients and PK were assessed after one dose and at SS.

RESULTS: Single dose and SS PK with and without food are summarized below (age for all=11.5±4.3). In addition, preliminary CYP2C9 genotypic data is available for 4 patients. 2 were CYP2C9*1*1(wildtype) consistent with the extensive metabolizer phenotype, 1 was CYP2C9*1*2 (intermediate metabolizer) and 1 was CYP2C9*3*3 (poor metabolizer). These data correlate well with observed PK parameters.

	n	t_{max} (h)	C_{max} (μg/L)	$AUC_{0-\infty}$ (μg/L·h)	$t_{½}$ (h)
Single dose-no food	21	3	1287.9±858.6	9201.9±5699.3	4.9±1.9
SS-no food	16	3	1439.8±755.6	11007.0±5201.2	5.0±2.4
Single dose-with food	3	3	2628.8±996.0	11546.4±1291.4	3.5±0.8
SS-with food	3	3	2439.8±912.8	13551.6±354.4	4.0±0.2
Single dose-CYP2C9*3*3	1	3	2940.4	108250.6	29.9
SS-CYP2C9*3*3	1	3	8468.7	549212.5	41.2

CONCLUSIONS: As previously reported, we confirm that significant differences exist between children and adults with respect to celecoxib disposition. We also show that food co-administration increases systemic exposure. Additionally, CYP2C9 genotyping in this small group of patients correlates well with the PK variation observed especially in the CYP2C9*3*3 patient who demonstrated a drastically reduced clearance capability. *Supported by Pfizer/Pharmacia Canada*

PI-109

CLINICAL PHARMACOLOGY OF TEZOSENTAN, A DUAL ENDOTHELIN RECEPTOR ANTAGONIST, IN PATIENTS WITH LIVER CIRRHOSIS. J. Dingemanse, PhD, PharmD, A. Halabi, MD, P. Hoever, MSc, H. Chadha-Boreham, PhD, P. L. van Giersbergen, PhD, Actelion Pharmaceuticals Ltd, IKP, Allschwil, Switzerland.

Tezosentan (T) is a dual endothelin (ET) receptor antagonist, formulated for parenteral use and excreted unchanged in bile. Since ET-1 may play a role in the pathogenesis of ascites and portal hypertension, cirrhosis and its complications may form an indication for T. The objectives of this study were to explore the tolerability, pharmacokinetics, and pharmacodynamics of T in patients with moderate/severe liver cirrhosis (Child-Pugh B-C). Each patient (total n=25) received 2 consecutive 24-h infusions of 0.2 and 1.0 or 1.0 and 5.0 mg/h of T or placebo. Blood pressure was monitored and blood samples were taken for measurement of T and ET-1. T was well tolerated (mainly mild headache as adverse event) and induced small dose-dependent reductions in blood pressure. T showed dose-proportional, 2-compartment pharmacokinetics: rapid distribution and slower elimination. Its exposure was dependent on the baseline bilirubin level. For bilirubin levels < 3 and 3.5-12 mg/dl, the exposure to T was 3.3 and 8.5 fold that in healthy subjects (historical control), due to reduced clearance. Compared to patients with acute heart failure, the relative exposure was 1.2 and 3.2 fold, respectively. Exposure to ET-1 increased dose proportionally and an indirect response model could describe the relationship between T and ET-1. The IC50 was independent of the severity of the disease. In conclusion, adjustment of the dosing regimen of T in cirrhotic patients, based on bilirubin levels, is warranted.