PI-156

ASSESSMENT OF MILK THISTLE AND BLACK COHOSH SUPPLEMENTATION ON DIGOXIN PHARMACOKINETICS. B. J. Gurley, PhD, M. A. Hubbard, MS, G. Barone, MD, Y. Tong, MS, D. K. Williams, PhD, J. Carrier, PhD, I. Khan, PhD, University of Arkansas for Medical Sciences, University of Arkansas, University of Mississippi, Little Rock, AR.

BACKGROUND: Phytochemical-mediated modulation of p-glycoprotein (P-gp) and other drug transporters may underlie many herb-drug interactions. Serial plasma concentration-time profiles of digoxin (DIG) (a P-gp substrate) were used to determine whether supplementation with milk thistle (MT) or black cohosh (BC) modulated P-gp activity in vivo.

METHODS: Sixteen healthy volunteers were randomly assigned to receive each supplement, on separate occasions, for 14 days followed by a 30-day washout period. Subjects were also randomized to receive rifampin (RIF) (600 mg daily for 7 days) and clarithromycin (CLT) (1000 mg daily for 7 days) as positive controls for P-gp induction and inhibition, respectively. DIG (Lanoxicaps, 0.4 mg) was administered orally before and at the end of each supplementation and control period. Serial DIG plasma concentrations were obtained over 24 hours. Comparisons of AUC, Cmax, and Tmax were used to assess the effects of MT, BC, RIF, and CLT on DIG pharmacokinetics.

RESULTS: RIF produced significant reductions ($p<0.01$) in AUC and Cmax, while CLT increased these parameters significantly ($p<0.01$). No statistically significant effects on DIG pharmacokinetics were observed following supplementation with either MT or BC, although BC approached significance for AUC ($p = 0.05$).

CONCLUSIONS: When compared to RIF and CLT, supplementation with MT or BC did not appear to affect DIG pharmacokinetics, suggesting that these supplements are not potent modulators of P-gp in vivo.

PI-157

INHIBITORY EFFECT OF STIRIPENTOL ON CLOBAZAM METABOLISM BY CDNA-EXPRESSED HUMAN CYP. A. Tran, PharmD, PhD, C. Giraud, E. Rey, PharmD, J. Vincent, PharmD, J. Treluyer, MD, PhD, G. Pons, MD, PhD, Ecole Pratique des Hautes Etudes, Hôpital Saint-Vincent-de-Paul, Biocodex, Paris, France.

OBJECTIVE: To characterize *in vitro* the interaction observed *in vivo* between stiripentol (STP), an anticonvulsant agent that inhibits the activity of several cytochromes P450 (CYP), and clobazam (CLB), a 1,5-benzodiazepine used in association with STP in Severe myoclonic epilepsy in infancy.

METHODS: cDNA expressed CYP3A4 and CYP2C19 (main P450 involved in CLB metabolism, Giraud et al.2004) were used to calculate Ki and IC_{50} of stiripentol in comparison with ketoconazole (CYP3A4 inhibitor) and omeprazole (CYP2C19 inhibitor).

RESULTS: STP inhibited N-demethylation of CLB to N-desmethylclobazam (NCLB) mediated by CYP3A4 (non-competitively) and CYP2C19 (competitively) with $Ki=1.59\pm 0.07$ and $0.516\pm 0.065\mu M$ and $IC_{50}=1.58\ \mu M$ [CI95%=1.20–2.08] and 3.29 μM [CI95%=1.87–5.79] respectively. STP inhibited also more strongly the hydroxylation of NCLB to 4'-hydroxy-N-desmethylclobazam by CYP2C19 (competitive- interaction with $Ki=0.139\pm 0.025\ \mu M$ and $IC_{50}=0.276\ \mu M$ [CI95%=0.206–0.371]). The inhibitory effect of STP on CLB demethylation by CYP3A4 was much weaker than that of ketoconazole (ketoconazole $IC_{50}=0.023\ \mu M$ [CI95%=0.016–0.033]) while its effect on NCLB hydroxylation by CYP2C19 was much higher than that of omeprazole (omeprazole $IC_{50}=2.99\ \mu M$ [CI95%=2.11–4.24]).

CONCLUSIONS: The major inhibitory effect of STP on CLB and mostly NCLB biotransformations *in vitro* is consistent with the changes of CLB and NCLB plasma concentrations observed *in vivo* in children treated by the association CLB/STP.

PI-158

ALVIMOPAN PHARMACOKINETICS (PK) & PHARMACODYNAMICS (PD) IN PATIENTS WITH CHRONIC CONSTIPATION (CC). V. D. Schmith, PhD, W. Garnett, PharmD, W. H. Barr, PharmD, PhD, D. Kelleher, PhD, M. Young, PhD, G. Sanderlin, S. Coots, A. Agyemang, G. Dukes, PharmD, GlaxoSmithKline, VCU Center for Drug Studies, Research Triangle Park, NC.

BACKGROUND: To characterize the PK/PD of alvimopan and its active metabolite (ADL 08–0011) in CC patients.

METHOD: Twenty females/three males with CC received placebo or 3 mg alvimopan (a peripherally-acting μ-opioid antagonist) BID for 7 days in a double-blind, randomized, crossover study. The PK of alvimopan & metabolite were characterized. Whole bowel transit (WBT) & mean colonic transit time (MCTT) were determined. Total bowel movements (BM) & spontaneous complete BM (SCBM) were recorded. Safety was monitored. PD assessments were reported previously.[a]

RESULTS: The geometric mean steady-state (SS) AUCτ, Cmax, & Cmin of alvimopan were 10.7 ng*hr/mL, 2.1 ng/mL, & 0.3 ng/mL, respectively. Metabolite concentrations were variable. Metabolite concentrations were at steady-state (SS) in ~50% of subjects on day 6 and were higher in patients that were at SS than those not at SS (AUC12 = 98 and 48 hr*ng/mL, respectively). The relationship between concentrations of alvimopan or metabolite and response (WBT, MCTT, BM or SCBM) was explored. Simulations were used to predict doses to be used in further clinical trials.

CONCLUSION: Alvimopan PK in CC patients was similar to healthy volunteers, although Cmin was higher in CC patients. Metabolite concentrations were variable, but were in the range of those predicted. The relative contribution of plasma concentrations of parent and metabolite to activity remains unclear in CC.

[a] Garnett, et al Digestive Diseases Weekly Poster 10029, 2004

PI-159

THE BIOEQUIVALENCE OF ORAL ADMINISTRATION OF TELITHROMYCIN TABLETS CRUSHED VERSUS SWALLOWED WHOLE IN HEALTHY ADULT SUBJECTS. C. L. Lippert, PhD, S. Gbenado, MS, C. Qiu, PhD, B. Lavin, MD, S. J. Kovacs, PharmD, Quintiles Inc., Aventis Pharmaceuticals, Kansas City, MO.

BACKGROUND/AIM: To establish bioequivalence of telithromycin (TEL) crushed versus whole tablet administration.

METHODS: Open-label, single-dose, randomized, 2-period, crossover study with a 6-day washout between periods: Treatment A: TEL 800 mg (2 × 400-mg tablets), swallowed whole with 240 mL water; Treatment B: TEL 800 mg (2 × 400-mg tablets), crushed and mixed in 240 mL Ensure®, followed by 120 mL water. Blood samples were collected predose and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, and 24 hpostdose. Plasma was assayed for TEL concentration by LC/MS/MS. Exposure measures were computed by noncompartmental methods using WinNonlin® (Pharsight Corporation). C_{max} and $AUC_{(0-24)}$ were determined from observed data. Average bioequivalence criteria was applied.

RESULTS: 32 subjects (16 M, 16 F) completed the study. 90% confidence intervals for the mean ratio of $AUC_{(0-24)}$ and C_{max} were within the 0.80–1.25 range. Median T_{max} was also similar between treatments (3.00 hours for each treatment). Both methods of administration were safe and generally well tolerated.

CONCLUSIONS: Crushing telithromycin tablets administered with Ensure is bioequivalent to administration of whole tablets. Breaking or crushing telithromycin tablets can be a viable alternate method of administration for patients unable to swallow whole tablets.

	Geometric Least Squares Mean		Mean Ratio (Treatment B/ Treatment A)	
	Whole (Treatment A)	Crushed (Treatment B)	Estimate	90% CI
N	32	32	-	-
$AUC_{(0-24)}$ (μg · h/mL)	7.493	7.862	1.049	(0.966, 1.139)
C_{max} (μg/mL)	1.324	1.255	0.947	(0.854, 1.051)

AUC_{0-24} = area under the concentration time curve from 0 to 24 h; CI = confidence interval; C_{max} = peak concentration.