

PI-129

LACK OF CLINICALLY SIGNIFICANT INTERACTION BETWEEN STEADY STATE TOLVAPTAN AND DIGOXIN IN HEALTHY VOLUNTEERS. S. E. Shoaf, PhD, Z. Wang, MD, S. Mallikaarjun, PhD, P. Brimont, PhD, S. L. Bramer, PhD, Otsuka MD Research Institute, Rockville, MD.

Tolvaptan (TLV) is a selective vasopressin receptor (V_2) antagonist being studied for several indications. Digoxin (DIG) is expected to be frequently co-administered with TLV. The objectives of this study were to determine the effect of TLV administration on steady state DIG pharmacokinetics (PK) and the effect of DIG on TLV PK. This study was an open-label, sequential design in 14 healthy men and women. Subjects received a single dose of 60 mg TLV on Day 1 followed by a 3-day washout. Following digoxin loading doses on Day 4, subjects received 0.25 mg DIG QD on Days 5 through 16. On Days 12 through 16, subjects also received 60 mg TLV QD. Plasma concentrations of TLV and metabolite were determined by HPLC-MS/MS. Serum and urine DIG were determined by turbidometric immunoassay. The table below summarizes the ratios of the C_{max} and AUC_{0-24h} geometric means and their 90% confidence intervals (90% CI) for steady state DIG+TLV vs. DIG alone and for a single oral dose of TLV with steady state DIG vs. TLV alone.

| Analytes | Parameter | C_{max} | AUC_{0-24h} |
|-----------|---------------------|-------------|---------------|
| Digoxin | Day 16/Day 11 Ratio | 1.27 | 1.18 |
| | 90% CI | 1.085-1.496 | 1.073-1.286 |
| Tolvaptan | Day 12/Day 1 Ratio | 1.11 | 0.97 |
| | 90% CI | 0.885-1.395 | 0.758-1.251 |

Although plasma DIG concentrations were elevated, there were no clinically relevant changes in body weight, heart rate, systolic or diastolic blood pressure, ventricular rate or QTc (Bazett's) interval between Day 11 (DIG alone) and Day 16 (DIG + TLV). Therefore, there is no clinically significant interaction between DIG and TLV.

PI-130

CLOBAZAM METABOLISM BY C DNA-EXPRESSED HUMAN CYP. G. Pons, MD, PhD, C. Giraud, A. Tran, PharmD, PhD, E. Rey, PharmD, J. Treluyer, MD, PhD, Pharmacologie, Université René Descartes, Hôpital Saint-Vincent de Paul, Assistance Publique-Hôpitaux de Paris and Ecole Pratique des Hautes Etudes, Paris, France.

Objective: Clobazam (CLB) is a 1,5 benzodiazepine effective as antiepileptic agent, mainly as add-on therapy in patients with refractory epilepsy. The aim of the study was to determine the main cytochromes P450 (CYP) involved in the metabolism of clobazam.

Methods: cDNA-expressed human CYP (1A1, 1A2, 2A6, 2B6, 2C8, 2C9, 2C18, 2C19, 2D6, 2E1, 3A4, 3A5 and 3A7) were used in vitro. Kinetic parameters K_m and V_m were calculated for the main metabolic pathways. Inhibition studies were conducted in human liver microsomes with specific inhibitors (furafylline, thiotepa, sulfaphenazole, omeprazole, quinidine, chlorzoxazone, and ketoconazole).

Results: CLB was mainly metabolized into desmethylclobazam (NCLB) by CYP3A4 and CYP2C19 ($K_m=29.0$ and $31.9\mu M$, $V_m=6.20$ and 1.15 nmol/min/nmolCYP, $V_m/K_m=214$ and 36.1 nmol/min respectively). NCLB was subsequently metabolized to hydroxy-desmethylclobazam (OH-NCLB) by CYP2C19 ($K_m = 5.74\mu M$, $V_m=0.219$, $V_m/K_m=38.2$ nmol/min). Hydroxylation of CLB into hydroxyclobazam and demethylation of hydroxyclobazam into hydroxy-desmethylclobazam were minor pathways.

The demethylation of CLB was inhibited by ketoconazole ($1\mu M$) at 74%, omeprazole ($10\mu M$) at 21% and thiotepa ($10\mu M$) at 20%. The hydroxylation of NCLB was inhibited by omeprazole ($10\mu M$) at 55% and ketoconazole ($1\mu M$) at 29%.

Conclusion: For the first time, the main metabolic pathways of clobazam were characterized: main pathways were demethylation of CLB by CYP3A4 and CYP2C19 and hydroxylation of NCLB by CYP2C19.

PI-131

EFFECT OF CHRONIC HEART FAILURE ON THE PHARMACOKINETICS OF EPLERENONE FOLLOWING SINGLE AND MULTIPLE DOSING. W. R. Ravis, PhD, S. Reid, MEd, P. J. Van Ess, PhD, J. Ferry, PhD, D. Tolbert, PhD, Auburn University, Pfizer, Inc, Auburn, AL.

This study determined the effect of chronic congestive heart failure (CHF) on the single- and multiple-dose pharmacokinetics of eplerenone (EPL). EPL is a highly selective aldosterone blocker indicated for the treatment of hypertension with demonstrated morbidity/mortality benefits in acute myocardial infarction patients with left ventricular heart failure. Eight subjects with CHF and 8 matched-control subjects (matched for age, sex, and weight) were enrolled in a 2-period, open-label, single- and multiple-dose study. After a single 50-mg dose and multiple once daily 50-mg doses, pharmacokinetic parameters were determined for EPL, its inactive ring-open form, SC-70303, and the inactive metabolite, SC-71597. No statistically significant differences in any EPL, SC-70303, or SC-71597 pharmacokinetic parameters were observed between CHF and control subjects. Following multiple-dosing, EPL CL/F was insignificantly lower ($\leq 27.4\%$) in CHF subjects compared with control subjects resulting in an insignificant increase in EPL AUC ($\leq 37.7\%$) and C_{max} ($\leq 29.7\%$). As expected from the pharmacology of EPL, mean serum aldosterone and active renin values increased in both subject groups following administration of EPL. CHF subjects had a reduction in mean Na^+ retention scores from 1.88 pre- to 0.5 post-treatment. EPL was well tolerated in both subject groups. These results indicate that dose adjustment based on pharmacokinetic alterations does not appear necessary in CHF patients.

PI-132

PHARMACOKINETICS OF EPLERENONE AFTER SINGLE AND MULTIPLE DOSING IN SUBJECTS WITH AND WITHOUT RENAL IMPAIRMENT. W. R. Ravis, PhD, T. J. Stokes, MD, S. Reid, MEd, P. J. Van Ess, PhD, B. Roniker, MD, D. Sica, MD, D. Tolbert, PhD, Auburn University, Pfizer, Inc, Medical College of Virginia, Auburn, AL.

Eplerenone pharmacokinetics were studied in subjects with varying degrees of renal function after single (100 mg) and multiple doses (100 mg daily for 5 days). This open-label, parallel-group study enrolled 32 renally impaired subjects and 32 normal matches. Subjects were stratified based on CL_{cr} : normal $CL_{cr}>80$ mL/min; mild $CL_{cr}=50-80$ mL/min, moderate $CL_{cr}=30-49$ mL/min, or severe impairment $CL_{cr}<30$ mL/min; and hemodialysis. The pharmacokinetics of eplerenone and metabolites were determined from plasma and urinary results. Following single or multiple dosing, eplerenone AUC, C_{max} , CL/F, and CL/F/WT were not statistically different ($P\geq 0.093$) between renally impaired and normal subjects. Compared to normal subjects, eplerenone renal clearance was significantly decreased in subjects with moderate and severe impairment. Since $<2\%$ of eplerenone is excreted unchanged, decreases in renal clearance did not result in significant alterations in CL/F. Subjects with severe impairment displayed the greatest decrease (18%) in mean CL/F/WT as compared to normal matches. In subjects with end-stage renal failure, approximately 10% of the dose was removed after 4 hours of hemodialysis. Eplerenone was well tolerated in all subjects. Dose adjustment based on pharmacokinetic alterations does not appear necessary in patients with renal impairment; rather, dose adjustment for eplerenone in renal failure, as with spironolactone, should be based on its potential effect on serum potassium values.