PI-87

BUSPIRONE PHARMACOKINETICS IN AUTISTIC CHILDREN. D. Edwards, PharmD, D. C. Chugani, PhD, H. T. Chugani, MD, J. Chehab, M. Malian, J. V. Aranda, MD, PhD, Wayne State University, Children's Hospital of Michigan, NICHD-PPRU Network, Detroit, MI.

BACKGROUND/AIMS: PET studies of alpha[C-11]methyltryptophan show that brain serotonin synthesis is elevated between 2 and 6 years of age. This process is disrupted in autistic children suggesting that the 5HT1A agonist buspirone might be useful in treating autism. Since there are no published PK data in young children, we studied the disposition of buspirone in autistic children aged 2 to 6 years.

METHODS: Subjects (5 males, 3 females) received a single oral dose of buspirone solution [2.5 mg for 2–3 year olds (n=5); 5.0 mg for 4–6 year olds (n=3)]. Blood was collected for 8 hours and plasma assayed for buspirone and the major metabolite 1-pyrimidylpiperazine (1-PP) using LC-MS.

RESULTS: The mean peak concentration of buspirone was 1101 ± 827 pg/mL with a median tmax of 0.5 hours. Oral clearance (Cl/F) averaged 91.5 L/hr/kg with an elimination half-life of 1.5±0.15 hours. Peak concentrations of 1-PP were 5.7-fold higher than for buspirone with a metabolite half-life of 4.1 hours. There was no evidence of non-linearity in buspirone or 1-PP disposition over the dose range studied.

CONCLUSIONS: The data indicate extensive metabolism in young children. Plasma concentrations and PK parameters for buspirone and 1-PP were similar to values observed in older children receiving 7.5–15 mg doses. Doses of 2.5–5 mg should be appropriate for younger children.

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EFFECT OF MDR1 GENOTYPE (G2677T) ON THE DISPOSITION OF CIPROFLOXACIN IN ADULTS. J. C. Gorski, PhD, J. L. Renbarger, MD, R. Vuppalanchi, MD, M. Miller, PhD, R. E. Galinsky, PharmD, S. D. Hall, PhD, Indiana University School of Medicine, US FDA Office of Women's Health, Purdue University School of Pharmacy, Indianapolis, IN.

BACKGROUND: Some fluoroquinolone antibiotics are substrates of MDR1. The aim of this study was to assess the effect of MDR1 genotype on the disposition of ciprofloxacin (**C**).

METHODS: 24 volunteers weighing 66±10 kg (mean±SD) with a mean age of 33±19 yrs completed the study after giving written informed consent. A single oral dose of **C** (500mg) was given and serial blood samples obtained. Serum **C** concentrations were determined using HPLC with UV detection. MDR1 exon 21 genotype (G2677T/A) was determined using real time RT-PCR.

RESULTS: MDR1 homozygous variant (G2677T) subjects (n = 7) had a significantly ($p \leq 0.05$) reduced oral clearance of **C** compared to individuals with 1 or 2 wild-type alleles (36 ± 6 vs. 49.5 ± 14 L/h). AUC and C_{MAX} of **C** were significantly greater in homozygous variant individuals (14.0±2.1 mg × hr/L, 3.0±0.8 mg/L) compared to wild-type allele carriers (10.9 ± 3.3 mg × hr/L, 2.1 ±0.8 mg/L, $P < 0.05$).

CONCLUSION: MDR1 exon 21 homozyogous variant (G2677T) subjects have a reduced **C** clearance and may have an enhanced efficacy and increased incidence of adverse events.

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PI-89

CHARACTERIZATION OF P-GLYCOPROTEIN INHIBITION AT THE BLOOD BRAIN BARRIER BY KETOCONAZOLE AND QUINIDINE USING THE CENTRAL PHARMACODYNAMICS OF LOPERAMIDE AS AN INDICATOR OF BRAIN DISTRIBUTION. T. Fullerton, PharmD, M. Bednar, MD, PhD, P. Raava, MS, J. Legg, BS, D. Hoelscher, MD, D. Eckols, BS, M. Gibbs, PhD, Medical and Development Sciences, Pfizer Inc, PPD International, Groton, CT.

BACKGROUND: Loperamide (L) is a μ opioid agonist that does not cause central opiate effects, presumably due to P-glycoprotein (Pgp) mediated efflux from the brain. L is a substrate for both CYP3A and Pgp. Ketoconazole (K) is a potent inhibitor of CYP3A. Quinidine (Q) and K inhibit Pgp. This study evaluated the ability of L to induce opioid effects in the presence of K or Q.

METHODS: In a 2 part trial, 8 & 10 subjects were studied after the steady state K (400 mg QD) or single-dose Q (100, 400, 800 mg) arms. L doses up to 16 mg were studied. Subjects received oral morphine (M) 30 mg as a positive control. Pupil diameter was measured via pupilometry. PK and PD parameters were determined using WinNonLin.

RESULTS: PK and PD parameters (adjusted geometric means) for L 16 mg are noted in following table:

Rx	K + P	P + L	Q100 + L	Q400 + L	Q800 + L	K + L	M
L Cmax (μg/mL)	—	3.10	4.04*	5.58*	7.78*	16.0*	—
L AUC (μg*h/mL)	—	40.8	50.1*	67.3*	88.1*	208*	—
AUEC (mm*h)	3.2	6.7	11.8	14.4$^+$	7.31	10.6$^+$	25.2$^+$
Emax (mm)	0.81	0.81	0.61	1.17$^+$	0.79	0.97	2.49$^+$

* $p < 0.01$ vs P + L; + $p < 0.05$ vs. P.

PD effects for all Q doses and K + L treatments were less than for M ($p < 0.01$).

CONCLUSIONS: The combination of L and K or Q produced modest central effects. While Q was somewhat more potent than K at inhibiting blood-brain barrier (BBB) Pgp, the PD effect for both combinations was much less than M. These results suggest the clinical relevance of the interaction between L and either Q or K at the BBB is marginal.

PI-90

PROJECTION OF DOSES FOR QT-PROLONGATION STUDIES BASED ON MODELING OF THE WORST-CASE INHIBITION OF CYP3A. J. Y. Chien, PhD, S. D. Hall, PhD, S. A. Wrighton, PhD, Eli Lilly & Company, Indiana University, Indianapolis, IN.

AIMS: To project the probability of "worst-case scenario" for CYP3A-mediated ketoconazole (K) inhibition of CYP3A drugs based on modeling of pharmacokinetic inhibition effect to select doses for high-dose QT prolongation studies for a low extraction ratio (ER) Drug A (range: 0.01–0.03) and high ER Drug B (range: 0.5–1). Both of these drugs are orally absorbed and cleared by CYP3A by unknown fractions (fm).

METHODS: The predicted K portal vein and systemic concentration were used to drive its inhibitory effect on intrinsic clearance and bioavailability of Drugs A and B. Simulations were performed to test worst-case scenarios, including the duration of K dosing and the range of drug's fm and ER.

RESULTS: Performance of the model was assessed by comparing simulated trials to actual clinical trial results for A and B given with 200 mg K. The model well predicted the 2-fold (A) and 6-fold (B) AUC increases observed in the trials. Assuming worst-case fm and bioavailability, 400 mg K produced less than doubling of AUC compared to results at 200 mg K for both drugs; maximum inhibition was obtained following 3 daily K doses. Doses for QT studies were then selected to achieve the 90th or the 50th quantile of the distribution of AUC ratios, or a 4- and 8-fold exposure-multiple from the target clinical doses, for Drugs A and B, respectively.

CONCLUSIONS: Model-based projection of the probable worst-case CYP3A inhibition can be used for high-dose QT prolongation study design.