PI-8

EFFECT OF ITRACONAZOLE AND RIFAMPIN ON THE PHARMACOKINETICS AND PHARMACODYNAMICS OF EBASTINE IN RELATION TO CYP2J2*8 GENOTYPE. J. Shon, MD, C. Yeo, MD, K. Liu, PhD, S. Lee, PhD, I. Cha, MD, PhD, J. Shin, MD, PhD, Department of Pharmacology and Pharmaco-Genomics Research Center, Busan, Republic of Korea.

BACKGROUND: Ebastine, a nonsedative H_1 receptor antagonist, is completely metabolized to the dealkylated metabolite and carebastine, an active metabolite via hydroxylation (M-OH). The conversion of M-OH to carebastine and Des-BP pathway are mainly catalyzed by CYP3A4, whereas the oxidation of ebastine to M-OH is exclusively mediated by CYP2J2.

AIMS: To evaluate the effect of itraconazole and rifampin on the PK and PD of ebastine in relation to CYP2J2*8 genotype.

METHODS: In open, 3-way crossover with a 2-week washout, 4 healthy subjects with wild type and 3 with heterozygous mutation for CYP2J2*8 were pretreated with itraconazole for 6 days, rifampin for 10 days, or not. A single oral dose of 20 mg ebastine was administered to subjects and blood to 72hrs and urine to 24hrs were collected. Histamine-induced wheal and flare reactions were measured to assess the effects on the antihistamine response to 12hrs.

RESULTS: The PK parameters of ebastine and active metabolite, carebastine, showed statistically significant change by pretreatment with itraconazole and rifampin. Itraconazole enhanced markedly the ebastine's inhibitory effect against histamine-induced skin reactions and rifampin pretreatment decreased that.

CONCLUSION: Itraconazole and rifampin pretreatment significantly altered the disposition and antihistamine effect of ebastine and carebastine in human. However, the genotype of CYP2J2*8 seems to have little effect on those even in the inhibited and induced state of CYP3A4.

PI-9

DOSE RANGING STUDY OF A NON-PESTICIDE LICE ASPHYXIATOR FOR THE TREATMENT OF HEAD LICE. J. T. Mitchel, PhD, M. Vicaria, D. H. Eyerdam, T. M. Meinking, Target Health Inc., Global Health Associates of Miami, New York, NY.

Pediculosis is increasing rapidly in the US and throughout the world due to drug resistance. This new investigational treatment for head lice, L.A. is pesticide free, works as a suffocant, will not cause resistance, and is environmentally safe. The mechanism of action of L.A. is to stun the respiratory spiracles open, thus enabling the treatment to mechanically block the respiratory system. Two randomized, observer-blinded, dose ranging Phase II clinical trials were conducted to evaluate the safety and efficacy of L.A. There were two treatments of 10 minutes each, one week apart. Subjects came from an area of high lice infestation. There were 81 subjects who entered and 79 who completed study 1; 42 subjects were entered and 39 completed study 2. The primary efficacy variable was the % of subjects with treatment success at the end of the study. On Day 1 post-treatment in Study 1, L.A. (5% and 10%) and RID treatment groups had $\leq$2.0 mean live lice, while the vehicle placebo group had a mean of 7.7 live lice ($p=0.004$). Kill rate was $>$80% in those receiving active treatment compared to $<$20% in the placebo group ($p<0.001$). At Day 15, all treatments demonstrated 70% success. In the minimum effective dose study, the hair was fully saturated during treatment. Results showed that 5% and 2.5% L.A. demonstrated an overall treatment success of 90.5% and 81.0%, respectively. Five subjects experienced expected adverse events during study 1, and 1 subject in study 2. The L.A. 5% treatment was efficacious and the dose of choice.

PI-10

CYP2D6 GENOTYPE AND PAROXETINE PHARMACOKINETICS IN THE ELDERLY: A POPULATION PHARMACOKINETICS ANALYSIS IN DEPRESSED GERIATRIC SUBJECTS. Y. Feng, MS, B. G. Pollock, MD, PhD, R. E. Ferrell, PhD, M. A. Kimak, C. Reynolds III, MD, R. R. Bies, PharmD, PhD, Department of Pharmaceutical Sciences, School of Pharmacy, University of Pittsburgh, Rotman Research Institute, Baycrest Hospital, University of Toronto; Department of Psychiatry, School of Medicine, University of Pittsburgh, Department of Human Genetics, School of Public Health, University of Pittsburgh, Department of Psychiatry, School of Medicine, University of Pittsburgh, Department of Pharmaceutical Sciences, School of Pharmacy, University of Pittsburgh, Department of Psychiatry, School of Medicine, Pittsburgh, PA.

AIM: To develop a population pharmacokinetic (PK) model using sparse data sampling from a geriatric depressed population with five-year paroxetine treatment and to identify significant covariates affecting disposition.

METHODS: Geriatric patients (age $\geq$ 70) with major depressive disorder treated with paroxetine from the five-year Maintenance Therapies in Late-Life Depression trial provided paroxetine concentration samples. A nonlinear mixed effects model was developed with NONMEM® for these subjects. The covariates, including CYP2D6 genotype, age, weight, sex, and race effect on pharmacokinetics were tested. One and two compartment models with linear and nonlinear elimination (Michaelis-Menten) were evaluated.

RESULTS: Total of 171 geriatric patients provided 1970 paroxetine concentrations for NONMEM analysis. A two-compartment nonlinear PK model with additive and proportional error provided the best model description. Weight and CYP2D6 polymorphisms had a significant effect on maximal elimination velocity (Vm) and sex on volume of distribution of the central compartment (V_2). The Vm estimates in the final PK model in each CYP2D6 genotype groups were: 125 μg/h in poor metabolizers, 182 μg/h in intermediate metabolizers, 454 μg/h in extensive metabolizers, and 3670 μg/h in ultra-rapid metabolizers.

CONCLUSIONS: CYP 2D6 polymorphisms and weight significantly affected the maximum elimination rate and sex significantly affected the V_2 in this elderly depressed patient population.

PI-11

ANTICHOLINERGIC DRUG BURDEN ASSOCIATED WITH PHYSICAL DISABILITIES. Y. Cao, D. E. Mager, E. M. Simonsick, S. Ling, G. Windham, L. P. Fried, D. R. Abernethy, Division of Clinical Pharmacology, Johns Hopkins School of Medicine, Baltimore, MD, University of Buffalo School of Pharmacy, Buffalo, New York, Institute on Aging Intramural Research Program, National Institute on Aging, National Institutes of Health, Baltimore, MD, Geriatric Medicine, Johns Hopkins University, Baltimore, MD.

BACKGROUND/AIMS: Expert consensus-derived lists or numbers of drugs prescribed are two current approaches to evaluate appropriateness of drug therapy for older patients. We hypothesized that drugs with anticholinergic and/or sedative properties contribute to drug exposure related morbidity, and that development of a drug burden index to characterize extent of exposure to these drugs would have utility to predict drug-induced disability independent of disease and other potential confounders.

METHODS:

Design: Cross-sectional study. Multivariate logistic regression.

Setting: Home visits and medical records.

Participants: Women aged 65+ years from the Women's Health and Aging Study (WHAS I) in Baltimore, Maryland.

RESULTS: Drug burden based on pharmacodynamic principles was defined. A strong independent relation between anticholinergic burden and greater activities of daily living difficulty, poorer balance, chair stands, mobility, gait speed, MMSE performance, difficulty of upper extremity function, and weaker grip strength was demonstrated. Sedative burden was only associated with impaired grip strength and mobility.

CONCLUSIONS: (1) Burden of multiple drugs can be quantified with the recommended dose regimen and the actual dose and frequency of drug taken. (2) Anticholinergic burden is strongly associated with impaired performance of a variety of functions important to independent living. Sedative burden results in impairment of a more limited array of functions.