PII-97

POPULATION PHARMACOKINETICS OF INTRAVENOUS VALPROIC ACID IN KOREAN PATIENTS. D. Yim, MD, PhD, H. Park, MD, College of Med. The Catholic Univ. of Korea, Gachon Medical School, Seoul, Korea.

Purpose. To determine population-based pharmacokinetic parameters for intravenous valproic acid, and the factors influencing these parameters, in Korean adults.

Methods. Valproic acid concentrations were obtained using a peak and trough sampling scheme for 102 Korean epileptic patients who were not taking concurrent antiepileptic medication. Three hundred and fifty-four serum concentrations were analyzed according to a one-compartment model with a mixed effect modeling method (NONMEM Ver 5.0). The influence of body-weight (kg), height, daily valproic acid dose (mg/day), body mass index (kg/m^2), sex, and age on Vd and CL was assessed in the course of analysis.

Results. Vd and CL of valproic acid increased with body-weight. No significant influence of the other screened covariates was observed. The final regression model was:

$CL\ (L/h) = 0.849 \times (\text{body-weight} / 60)^{0.702}$

$Vd\ (L) = 15.1 \times (\text{body-weight} / 60)^{0.604}$

Interindividual variabilities (coefficient of variation) for CL and Vd were 32% and 18%, respectively. Residual error including intra-individual variability was 26.7%.

Conclusion. The current results may be used as a basic reference to optimize drug therapy with intravenous valproic acid. Further research on the pediatric population is necessary to confirm the nonlinearity of the relation between body-weight and Vd.

PII-98

SAFETY AND TOLERABILITY AND ABSORPTION OF TOPICAL THALIDOMIDE. S. M. Gordon, DDS, MPH, S. M. Wahl, PhD, C. Picco, BS, R. A. Dionne, DDS, PhD, NIH, NIDCR, Bethesda, MD.

The adverse effects of thalidomide are well known, but there are no published data on the safety, tolerability, and absorption of low doses delivered by the topical route. This study evaluated the safety and tolerability of topical thalidomide applied to oral mucosa and determined the amount of drug reaching systemic circulation. Subjects were HIV+ pts with oral ulcers and age-matched healthy volunteers receiving 0, 5, 10, or 20 mg topical thalidomide applied to intact buccal mucosa in a randomized, double-blind design. Blood drawn serially was measured for thalidomide by HPLC using UV detection. The 20 mg dose was detectable in plasma 5 min post application and peaked at 1 hr in HIV+ pts with oral ulcers, whereas the same dose was detectable only at 3 hr in healthy volunteers. The remaining doses were below the level of reliable quantitation. The difference in detection of 20 mg of topical thalidomide in the healthy subjects versus the HIV+ pts with oral ulcers indicates that drug absorption was facilitated by the inflamed and disrupted mucosa. There were no significant differences in side effects between placebo and any dose group. Viral load did not change in HIV+ pts over the course of several weeks of treatment and there was no incidence of or change in neuropathy. The low plasma concentration and negligible incidence of adverse effects in both subject groups suggests topical thalidomide may be active at a lower dose while minimizing absorption and adverse effects.

PDI-A-1

LACK OF GENOTYPE:PHENOTYPE ASSOCIATIONS BETWEEN CYP3A4*1B, CYP3A5*3C, CYP3A5*6 AND MIDAZOLAM METABOLISM IN EUROPEAN- AND AFRICAN-AMERICANS. M. Floyd, MD, G. Gervasini, PhD, K. Bhat, PhD, A. George, MD, G. Mayo, RN, G. R. Wilkinson, PhD, DSc, G. Wilkinson, PhD, DSc, Vanderbilt University, Nashville, TN.

The determinants of interindividual variability in basal and induced CYP3A activity are unclear. Identification of common genetic variants, some with functional consequences, suggest a possible molecular mechanism. Thus, midazolam's disposition after intravenous and oral administration was determined in 70 healthy subjects, substratified about equally according to sex and racial ancestry (European- *versus* African-American), genotyped for *CYP3A4*1B,CYP13A5*3C* and *CYP3A5*6* alleles. Studies were performed prior to and after 21 days administration of rifampin (600 mg daily). Neither sex- nor population-related differences in midazolam's clearances were observed with either route, before or after rifampin treatment. Also, no differences in midazolam's clearances were noted between any homozygous wild-type or mutant groups and no gene-dose effects were observed for any of the variants. Rifampin treatment produced marked induction, however, its extent did not appear to be related to any specific genotype. It, therefore, appears that the studied genetic variants are not contributory to intersubject variability in CYP3A activity (supported by GM31304).

PDI-A-2

CORRELATION OF PHARMACOGENETIC GENOTYPE WITH STEADY-STATE METABOLIC PROFILES OF TAMOXIFEN: EFFECT ON ACTIVE METABOLITE CONCENTRATIONS. K. Lee, MD, PhD, Z. Desta, PhD, V. Stearns, MD, D. F. Hayes, MD, D. R. Jones, PhD, D. A. Flockhart, MD, PhD, Sungkyunkwan University College of Medicine, Samsung Medical Center, Indiana University, School of Medicine, University of Michigan, Suwon, Korea.

To test the hypothesis that pharmacogenetic factors might alter tamoxifen (TAM) metabolism to active metabolites, a prospective clinical trial was conducted in 28 women who were taking oral tamoxifen (20mg/day) chronically for the treatment or prevention of breast cancer. TAM and its metabolites were measured in plasma after 4 months of the drug administration by high-performance liquid chromatography with on-line derivatization and genotypes for CYP2C9 (*2 and *3), CYP2C19 (*2 and *3), CYP2D6 (*3, *4, *6, *8, *10, and *17), and CYP3A5 (*3 and *6) were determined. The genotypes for CYP2C9, CYP3A5, and CYP2C19 did not correlate separately, or in any combination with plasma concentrations of TAM or its metabolites. In contrast, the concentrations of 4-hydroxy-N-desmethyltamoxifen (4-OH-NDM) was significantly lower ($p=0.0003$) in the subjects ($n=8$) with CYP2D6*1/*4, CYP2D6*1/*6, or CYP2D6*4/*4 genotype compared with those in CYP2D6*1/*1 or CYP2D6*1/*10 genotype ($n=20$). Accordingly, the molar concentration ratios of 4-OH-NDM/NDM and 4-OH-NDM/TAM in the subjects who have CYP2D6*4 or CYP2D6*6 variant allele(s) were significantly lower compared with those in CYP2D6*1/*1 or CYP2D6*1/*10 ($p=0.0061$ and $p=0.0010$, respectively). In addition, the molar concentration ratio of 4-OH-NDM/4-OH-TAM in the subjects who have CYP2D6*4 or CYP2D6*6 variant allele(s) were significantly higher compared with those in CYP2D6*1/*1 or CYP2D6*1/*10 ($p=0.0002$).