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PHARMACOKINETIC POPULATION MODELING OF NICOTINE INCORPORATING CYP2A6 GENOTYPES FOLLOWING DIFFERENT ROUTES OF ADMINISTRATION. Y. Yoon, MD, PhD, D. Verotta, PhD, N. Benowitz, MD, University of California San Francisco, Inje University (Korea), San Francisco, CA.

PURPOSE: We developed a comprehensive population pharmacokinetic (PK) model to quantify the influence of CYP2A6 genetic polymorphisms (GP) and covariates (COV) on the PK of nicotine following different routes of administration, and to predict individual subjects' PK.

METHODS: Two groups of 64 and 278 subjects received oral (OR) and IV administration of deuterium-labeled nicotine. Genotyping of CYP2A6 *(*1A, *1B, *1x2, *2, *4, *7,* and **9*) was carried out. CYP2A6 GP is incorporated using indicator variables (G_i): if a subject carries the *i-th* genotype G_i is 1, and it is 0 otherwise. The influence of CYP2A6 GP on clearance, e.g., is expressed as: $CL = \Sigma^{m}_{i=1}\ \theta_i G_i$, where m is the number of different genotypes. The analysis yields GP and COV influence on *CL, Q,* V_1, V_2 *(*IV) and *ka, CL/F, Q,* V_1/F *((*OR).

RESULTS: Body weight and age were significant COV for both IV and OR administrations. Smoking, marital status, education, BMI were not significant. The Asian group showed a significant decrease in clearance (52.8%) compared to other racial groups. Race was not significant after incorporating CYP2A6 GP. CYP2A6 **4/*4* decreased the clearance to 31.5 % of the wild-type clearance.

CONCLUSIONS: We elucidated the relationships between CYP2A6 GP and COV and nicotine clearance. We are developing the model to incorporate patch administration (PA) and developing a Bayesian model for OR and PA.

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OATP-C(OATP01B1)*15 IS ASSOCIATED WITH STATIN-INDUCED MYOPATHY IN HYPERCHOLESTEROLEMIC PATIENTS. K. Morimoto, MS, S. Ueda, MD, N. Seki, MD, Y. Igawa, MS, Y. Kameyama, MS, A. Shimizu, MS, T. Oishi, BS, M. Hosokawa, PhD, K. Iesato, MD, S. Mori, MD, Y. Saito, MD, K. Chiba, PhD, Chiba University, Nippon Kayaku Co, Ltd., The Japan Health Sciences Foundation, Chiba, Japan.

BACKGROUND: Statins are associated with muscle complaints ranging from myalgia to rhabdomyolysis. We studied the genetic contribution to the risk of the statin-induced myopathy by comparing frequencies of mutant alleles of candidate genes in case and control groups.

METHODS: We studied ten Japanese patients with abnormal increase in plasma creatinine kinase or severe muscle complaints, in comparison with control patients (n=26) who received statins but had no myopathy. DNA samples were genotyped for 152 SNPs/mutations in eight candidate genes selected from genes responsible for inherited rhabdomyolysis and those involved in the metabolism or transport of stains.

RESULTS: No mutations or SNPs were detected in the genes of inherited rhabdomyolysis except for 128G>A in *VLCAD,* of which frequency was almost the same as that of the controls. For *CYP3A4* and *MRP2,* one and two SNPs were detected respectively, but there was no significant difference between the groups. However, we found a significant association between *OATP-C*15* and pravastatin- or atorvastatin-induced myopathy ($P<0.01$). An odds ratio of 11.3 (95%CI=1.6–80.3, $P<0.05$) was obtained when the possession of one or more *OATP-C*15* was compared. In addition, an association between 2677G>A in *MDR1* and simvastatin- or atorvastatin-incuced myopathy was also observed ($P<0.05$).

CONCLUSIONS: The results suggest that *OATP-C*15* is one of the susceptible factors for development of myopathy in patients taking pravastatin or atorvastatin.

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PHARMACOGENETIC VARIANTS INFLUENCE TAMOXIFEN'S ESTROGENIC EFFECT ON BONE DENSITY. A. T. Nguyen, BSc, Y. Jin, MD, M. Rehman, MD, L. Li, PhD, T. C. Skaar, PhD, V. Stearns, MD, D. F. Hayes, MD, D. A. Flockhart, MD, PhD, Indiana University School of Medicine, John Hopkins School of Medicine, The University of Michigan, Indianapolis, IN.

BACKGROUND: Long-term effects from tamoxifen therapy for breast cancer include changes in bone mineral density (BMD).

METHODS: We examined the effects of menopausal status, tamoxifen and its metabolite concentrations on BMD in 69 women treated with 20mg of tamoxifen for one year. We tested for associations between genetic variants in *CYP2D6,* Estrogen Receptor α (ER) and change in BMD, measured in the lumbar spine and hip. Variants in CYP2D6 (*3, *4, *5, *6 and *10) and estrogen receptor (PvuII and XbaI) were identified by RFLP assays.

RESULTS: We noted a significant decrease in lumbar BMD in pre-menopausal women (Mean -0.069 ± 0.057 g/cm^2, p=.0001). No significant changes in post-menopausal women were found (p=.27). Pre-menopausal women with non-variant CYP2D6 genotypes experienced greater decrease in lumbar BMD than those who were *1/*4 or *4/*4 (p=.041). The active tamoxifen metabolite endoxifen was significantly correlated with lumbar spinal change in this pre-menopausal group ($r^2 = 0.22$, $p = 0.023$). ER variants did not predict these changes in BMD. In post-menopausal women who carried the ERα PvuII TT genotype there was a significant increase in hip BMD (Mean $+0.019 \pm 0.050$ g/cm^2, p=.023).

CONCLUSION: Pre-menopausal women experienced loss in lumbar spine BMD during tamoxifen treatment that was associated with *CYP2D6* wild-type genotype and high endoxifen concentrations. In post-menopausal women, ERα TT genotype was associated with an increase in hip BMD.

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HERITABILITY OF DIGOXIN PHARMACOKINETICS. D. L. Kroetz, PhD, T. Nguyen, BS, T. Giang, PharmD, L. Hodges, BS, R. Castro, MD, E. T. Lin, PhD, C. Brett, MD, G. Swan, PhD, University of California San Francisco, SRI, San Francisco, CA.

BACKGROUND/AIMS: The clinical significance of genetic variability in membrane transporters is still unclear. In this study, we compared digoxin pharmacokinetics in monozygotic (MZ) and dizygotic (DZ) twin pairs to test the hypothesis that genetic differences contribute to interindividual variability in digoxin disposition. Digoxin is minimally metabolized in humans and its bioavailability is highly dependent on drug transporters.

METHODS: Each twin pair (10 MZ and 6 DZ) was administered a 1 mg oral dose of digoxin and plasma and urine were collected over 3 days. Pharmacokinetic parameters were estimated using standard methods. A preliminary estimate of heritability was calculated using variability between and within the MZ twin pairs ($r_{GC} = (V_{between} - V_{within})/V_{between}$).

RESULTS: Preliminary estimates indicate that 36% of the variability in oral clearance (CL/F) can be attributed to genetics ($r_{GC} = 0.359$). In contrast, genetics accounts for only a minor component of the variability in CL_R ($r_{GC} = 0.19$). Data from DZ twin pairs will be used to estimate the true heritability index.

CONCLUSIONS: These studies suggest that digoxin oral clearance is influenced by both environmental and genetic differences among individuals. Future studies will determine the contribution of genetic polymorphisms in membrane transporters involved in digoxin bioavailability on interindividual variability in digoxin pharmacokinetics. Supported by NIH GM61390 and the Robert Black Charitable Foundation.