PII-21

INFLUENCE OF SEROTONIN RELATED GENES ON TAMOXIFEN INDUCED HOT FLASHES AND RESPONSIVENESS TO SELECTIVE SEROTONIN REUPTAKE INHIBITORS. J. Hwang, MD, Y. Jin, MD, A. M. Storniolo, MD, D. F. Hayes, MD, L. Li, PhD, V. Stearn, MD, T. C. Skaar, PhD, D. A. Flockhart, MD, PhD, Seoul National University Bundang Hospital, Korea, Clinical Pharmacology Hematology/Oncology, Indiana University, University of Michigan, Johns Hopkins University, Indianapolis, IN.

BACKGROUND: Hot flashes are the most common side effect in women treated with tamoxifen, but their severity is variable. Since serotonin is thought to be involved in hot flashes, we determined the association of hot flashes with polymorphisms of four serotonin related genes in women taking tamoxifen.

METHODS: We studied 190 breast cancer patients before and after 1 & 4 months of tamoxifen therapy. At each time point, hot flash frequency and severity and current medication were recorded. The 5-HTTLPR variant in serotonin transporter, C(-1019)G polymorphism in serotonin 1A receptor (HTR1A), T102C in serotonin 2A receptor (HTR2A), and A218C in tryptophan hydroxylase1 (TPH1) were studied. Associations were analyzed by log-linear regression with repeated measures.

RESULTS: Before tamoxifen therapy, premenopausal subjects with previous chemotherapy with 5-HTTLPR ss genotype had higher hot flash scores than those with ll or ls genotype ($P=0.04$). In peri & postmenopausal subjects, hot flash scores of ss genotype increased more during tamoxifen therapy ($P=0.02$) and HTR2A TT genotype had higher hot flash scores before ($P=0.02$) and after ($P=0.001$) tamoxifen therapy than TC and CC. SSRIs appeared to be less effective at reducing hot flashes in HTR2A TT genotype patients ($P=0.04$). HTR1A and TPH1 were not associated with hot flashes.

CONCLUSIONS: A pharmacogenetic interaction between tamoxifen and the serotonin transporter and HTR2A may contribute to the variability in tamoxifen induced hot flashes.

PII-22

STRUCTURE-ACTIVITY RELATIONSHIPS AND IN SILICO MODELING OF ACTIVATION OF THE HUMAN PREGNANE X AND VITAMIN D RECEPTORS BY BILE SALTS AND STEROID COMPOUNDS. M. D. Krasowski, MD, PhD, E. J. Reschly, PhD, M. Iyer, PhD, University of Pittsburgh, Pittsburgh, PA.

BACKGROUND/AIMS: The pregnane X receptor (PXR; NR1I2) is a nuclear hormone receptor with broad ligand specificity that regulates the metabolism and elimination of bile salts, steroid hormones, and xenobiotics. PXR is closely related to the vitamin D receptor (VDR; NR1I1), although VDR has much narrower ligand specificity. The purpose of the study was to compare structure-activity relationships for activation of the human PXR and VDR by 47 bile salts and 71 steroid hormones and to use in silico modeling to determine the role of ligand-binding pocket size, ligand orientation, and receptor flexibility in determining ligand activity.

METHODS: Activation of human PXR and human VDR was studied using an in vitro assay in HepG2 liver cells. In silico modeling of human PXR ligand activation was performed with 4D-QSAR analysis (Chem21 Group, Inc.) and comparative molecular field analysis (SYBYL with CoMFA, Tripos, Inc.).

RESULTS: Human PXR was activated by 25/47 bile salts and 58/71 steroids tested while human VDR was only activated by 5 bile salts. The concentrations of bile salts and steroids that activate human PXR are at least one, and often several, orders of magnitude higher than concentrations circulating in plasma in healthy humans.

CONCLUSIONS: Human PXR has very broad specificity but low affinity for bile salts and steroid compounds, consistent with a role in detecting toxic levels of these compounds. This broad specificity present significant challenges for in silico prediction of human PXR ligand activation.

PII-23

INFLUENCE OF OATP-C GENOTYPE ON THE PHARMACOKINETICS OF ROSUVASTATIN. H. Oh, BS, J. Choi, MD, M. Lee, MD, PhD, K. Park, PhD, MD, Yonsei University College of Medicine, Dept of Pharmacology, Seoul, Republic of Korea.

BACKGROUND: To investigate the influence of the Organic Anion-Transporting Polypeptide C(OATP-C) genotype on rosuvastatin pharmacokinetics.

METHODS: 121 healthy Koreans were examined with regard to the OATP-C∗1b/∗1b, OATP-C∗1b/∗15, and OATP-C∗15/∗15 genotype. The 3 genotypes were selected according to the study with 120 Japanese on pravastatin, where significant pharmacokinetic differences were observed among the 3 genotypes. Among 121 subjects, 13 subjects, 6 for ∗1b/∗1b, 6 for ∗1b/∗15, and 1 for ∗15/∗15, were selected for the rosuvastatin pharmacokinetic study of a single oral dose of 10mg. Blood samples were collected at 0, 0.5, 1, 3, 5, 7, 10, 15, 24, 48, 72hr after dosing. Using a noncompartment method, area under concentration-time (AUC), maximum concentration (Cmax), time to maximum concentration (Tmax) were calculated for the 3 genotypes.

RESULTS: AUC for ∗15/∗15 was 201.4 ng·h/ml, whereas those for the other 2 genotypes were about a half (111 ± 57 for ∗1b/∗1b and 106 ± 40 for ∗1b/∗15, value as mean $\pm$ SD) without significant difference each other ($p=0.85$). For ∗15/∗15, Cmax was also twice as much, but Tmax was smallest. For lactone, 1b/∗1b showed the highest value of AUC and Cmax among the 3 genotypes.

CONCLUSIONS: The results show that the genomic difference of OATP-C can influence rosuvastatin pharmacokinetics. A study with more subjects would be necessary to further support our results. Influence on pharmacodynamics and other genetic variations such as MRP2 and BCRP may also need to be investigated.

PII-24

LOW FREQUENCY OF THE CYP2D7-ACTIVATING 138delT POLYMORPHISM IN DIFFERENT ETHNIC GROUPS. A. Bhathena, PhD, T. Mueller, MS, D. R. Grimm, PhD, K. B. Idler, BS, A. C. Tsurutani, BS, D. A. Katz, PhD, Abbott Laboratories, Abbott Park, IL.

BACKGROUND: Polymorphisms within cytochrome P450 2D6 (*CYP2D6)* result in different metabolizer phenotypes, but some discordance suggests the possibility of additional unknown alleles or factors contributing to metabolism. A recent study showed a high frequency frameshift-causing deletion, *CYP2D7* 138delT, which converted the *CYP2D7* pseudogene to a functional gene within the brain.[1] The high frequency of the deletion and the resulting *CYP2D7* expression could have important implications for brain-specific metabolism of psychoactive substances. Our goal was to determine the frequency of this deletion in a larger ethnically diverse population.

METHODS: The *CYP2D7* 138delT genotypes for 163 Caucasians, 95 East Asians, 50 South Asians, 68 Hispanic Latinos, and 68 African Americans were determined by Pyrosequencing.

RESULTS: The 138delT allele was observed at a frequency of 1.0% in East Asians and 0.74% in Hispanic Latinos. The deletion was not observed in the other ethnic populations.

CONCLUSIONS: The very low frequency of the *CYP2D7* 138delT polymorphism in our panel is in contrast to the high frequency (50%) reported in the Indian population.[1] Our results suggest that *CYP2D7* 138delT is unlikely to be highly relevant for population variation of pharmacokinetics or drug response.

[1]Pai et al. (2004) *J Biol Chem* 279, 27383-27389.