PI-56

INTERACTION OF CLADRIBINE AND FLUDARABINE WITH GENETIC VARIANTS IN THE CONCENTRATIVE NUCLEOSIDE TRANSPORTER, CNT3. I. Badagnani, PharmD, and K. M. Giacomini, PhD, Department of Biopharmaceutical Sciences, University of California, San Francisco, CA.

The concentrative nucleoside transporter, CNT3 (SLC28A3), mediates the intracellular uptake of the anti-cancer nucleoside analogs, cladribine and fludarabine. Wide variation in intracellular levels of these analogs has been described. To test the hypothesis that coding variants in CNT3 may contribute to this phenotype, we identified and functionally tested missense variants of CNT3. Ten missense variants were found in a collection of 256 ethnically diverse DNA samples; three of these had total allele frequencies ≥1%. The activity of the missense variants was determined by isotopic uptake of model nucleosides in *X. laevis* oocytes expressing the CNT3 variants. The rare variant, CNT3-G>R, showed an 85% and 83% reduction in the transport of inosine and thymidine, respectively. All other variants had similar activity as the reference. There was no difference in the interaction kinetics of the three common variants with adenosine when compared to reference (Km=69±11, 91±24, 78±9, 94±3 μM for CNT3, CNT3-S>N, -Y>C and -I>V, respectively). These studies indicate that common missense variants of CNT3 have similar activities as the reference and suggest that they do not contribute to variation in intracellular levels of nucleosides and nucleoside analogs. Studies are underway to assess the interaction kinetics of nucleoside analogs with the common CNT3 variants and to test whether variation in CNT3 expression contributes to variation in intracellular levels of nucleoside analogs.

PI-57

THE EFFECT OF CYP2D6 GENOTYPE ON THE PHARMACOKINETICS OF LOVASTATIN IN CHINESE SUBJECTS. O. Q. Yin, PhD, Q. Chang, PhD, B. Tomlinson, MD, M. S. Chow, Pharm D, The Chinese University of Hong Kong, The Chinese University of Hong Kong, Shatin, NT, Hong Kong.

To investigate whether specific CYP2D6 genotype can influence the pharmacokinetics of lovastatin, a drug with multi-metabolic pathway (CYP3A4, 2C9, 2D6 and hydrolysis). A single 40 mg oral dose of lovastatin was administered to 19 healthy subjects. Multiple blood samples were collected over 24 h, and plasma concentrations of lovastatin and lovastatin acid (one of the major metabolites by hydrolysis) were determined by an LC-MS-MS method. CYP2D6 genotype was determined using PCR followed by restriction enzyme analysis or allele-specific PCR tests. The subject distribution were: 4 homozygous CYP2D6*1 (*1/*1), 7 heterozygous CYP2D6*10 (*1/*10 or *2/*10) and 8 homozygous CYP2D6*10 (*10/*10) carriers. The area under the plasma concentration-time curve ($AUC_{0\text{-}24}$) and terminal elimination half-life ($t_{1/2}$) of lovastatin among the three groups were 12.4±4.0, 20.2±10.4 and 30.0±10.5 ng•h/ml, and 4.4±0.9, 6.0±2.4 and 8.1±2.5 h respectively (one-way ANOVA, $p=0.022$ for $AUC_{0\text{-}24}$ and $p=0.046$ for $t_{1/2}$). In comparison to the homozygous CYP2D6*1 carriers, the oral clearance of lovastatin were lower by 32.5% ($p<0.05$) and 55.2% ($p<0.01$) in the heterozygous CYP2D6*10 and homozygous CYP2D6*10 carriers respectively. The $AUC_{0\text{-}24}$ of lovastatin acid also tended to be higher in the heterozygous CYP2D6*10 and homozygous CYP2D6*10 carriers; however, the difference was not statistically significant. These preliminary results in Chinese subjects show that among extensive metabolizers of CYP2D6, the pharmacokinetics of lovastatin appears to be dependent on CYP2D6 genotype.

PI-58

THE EFFECT OF POLYMORPHISM ON SEROTONIN AND HISTAMINE RESEPTOR IN ANTIPSYCHOTIC ACTION OF OLANZAPINE. T. Amamoto, MD, S. Nakaya, T. Kumai, PhD, Y. Morokawa, MD, PhD, K. Gen, MD, PhD, H. Suzuki, MD, PhD, T. Akimoto, MD, A. Aoba, MD, PhD, S. Kobayashi, MD, PhD, St. Marianna University School of Medicine, Kawasaki, Japan.

PURPOSE: There are individual differences in the effects of antipsychotic drugs. As the genetic polymorphisms of several reseptors are thought to be a cause of individual differences, we investigated the effects of the genetic polymorphisms in serotonin receptors, histamine receptor and serotonin transporter genes on the clinical outcome of olanzapine. **METHODS:** Patients of schizophrenia were enrolled simultaneously at St. Marianna University hospital with their written informed consent. In this study was approved by the institutional review board at St. Marianna University School of Medicine. Patients were given olanzapine (5~20mg) and blood were collected at 8weeks after drug administration. Clinical symptoms were evaluated by the PANSS scores before drug administration and at 4~8weeks of follow up. Genomic DNA were extracted from peripheral blood samples to analyze genetic polymorphisms 5HT2A (25Thr/Asp, 102T/C, 452His/Tyr, -1438G/A), 5HT2C (23Cys/Ser), 5HTTLPR (-1396 44bp Ins/Del), H2R (-1018G/A), by PCR-RFLP and the method of direct sequence. **RESULTS:** The polymorphic groups of 5HT2A (452His/Tyr, -1438G/A) and 5HT2C (23Cys/Ser) were prone to present better PANSS scores compared to the wild type group, whereas the group of 5HT2A(102T/C) showed insignificant results. It is necessary to analyze more number of cases.

PI-59

INTER- AND INTRAINDIVIDUAL VARIABILITY OF URINARY DEXTROMETHORPHAN/DEXTRORPHAN (DM/DX) RATIOS IN CYP2D6 EXTENSIVE METABOLIZERS (EMS) WITH ONE OR TWO ACTIVE ALLELES. J. D. Ma, PharmD, J. S. Bertino Jr., PharmD, A. Gaedigk, PhD, MS, A. D. Kashuba, PharmD, D. S. Streetman, PharmD, A. N. Nafziger, MD, MHS, Bassett Healthcare, Children's Mercy Hospital and Clinics, University of North Carolina, University of Michigan, Cooperstown, NY.

There is significant inter- and intraindividual variability of urinary DM/DX ratios. Distinguishing between CYP2D6 EMs with one or two active alleles may explain a portion of the observed variability. This study evaluated DM/DX ratios in CYP2D6 EMs for 1) differences by genotype and 2) intraindividual variability. Data from four previous studies were used. 62 healthy Caucasian adults genotyped and phenotyped as CYP2D6 EMs (38.6±7.6 yrs, 19M/40F) were administered oral DM≥2 times. 12-16 hour urine collections were assayed for DM and DX by HPLC. An unpaired t-test was used to evaluate differences in log-transformed DM/DX ratios by genotype. Coefficients of variation (CV%) were calculated to examine intraindividual variability of DM/DX ratios and were compared by Wilcoxon rank-sum test. 38 subjects had 2 active alleles (*1, *2) and 21 had 1 active and 1 null allele (*3, *4, *5). 3 subjects had 1 decreased activity allele (*10) and were not included. After 30mg of oral DM, there was no difference in DM/DX ratios [geometric mean (SD)] between subjects with 2 vs 1 active allele [0.0047 (0.0105, 0.0021) vs 0.0065 (0.0180, 0.0023); $p=0.23$]. After repeated doses of oral DM, CV% (median, range) of DM/DX ratios were not statistically different for those with 2 (41.0%, 4.3-136.6%) vs 1 active allele (44.5%, 6.0-105.5%) ($p=0.90$). Urinary DM/DX ratios cannot distinguish between CYP2D6 EMs with one or two active alleles.