

Besides several changes in HAART were needed due to resistance or persisting replication. After the last change in HAART (darunavir-ritonavir), voriconazole C_0 decreased to 0.25 mg/L (50% decrease). Eventually, ranitidine was replaced by esomeprazole 40 mg IV BID. Three days later, voriconazole C_0 increased 14-fold and voriconazole dose could be reduced by 50% to 100 mg (2.5 mg/kg) BID. There were no other medication changes. Subsequent voriconazole C_0 stayed within the therapeutic range.

Results: Voriconazole systemic exposure depends on various factors among which CYP 450 activity influenced by genetic polymorphisms and DDI. Our patient was heterozygous for the CYP2C19*17 variant allele, which has been associated with lower voriconazole AUC compared with wild-type individuals. However, her phenotype indicated a reduced activity of CYP2C19.

The change in voriconazole concentrations cannot be explained by a DDI with another drug of the antiretroviral treatment.

Conclusion: We report the case of an HIV patient with disseminated fungal disease who achieved targeted voriconazole C_0 using esomeprazole as a "booster" to overcome an ultrarapid CYP2C19*17/*1 genotype and a treatment by a CYP2C19 inducer such as ritonavir. Further evaluation is warranted for this "boosting strategy" to define the right booster dose, the relevance of this effect in rapid metabolizers and eventually transferability in clinical setting.

Disclosure of Interest: None declared.

PP135—PHARMACOMETABOLOMICS FOR INDIVIDUALIZED TREATMENT OF ALCOHOLISM: HIGH SERUM GLUTAMATE LEVEL IS ASSOCIATED WITH POSITIVE RESPONSE TO ACAMPROSATE TREATMENT

D.-S. Choi¹; H.W. Nam²; and V. Karpayak³

¹Pharmacology and Psychiatry; ²Pharmacology; and ³Psychiatry, Mayo Clinic College of Medicine, Rochester, United States

Introduction: Acamprosate, a homo-aurine analogue, is approved for treatment of alcohol dependence. Meta-analyses favor acamprosate for its ability to support abstinence, which is the most stable type of remission in alcoholics. Yet, only a limited number of treatment-seeking alcoholics use acamprosate, most likely because of individual differences in response and the lack of response predictors.

Patients (or Materials) and Methods: We used a pharmacometabolomics approach to investigate metabolic response in serum amino acid metabolites (including acamprosate) between responders and nonresponders to acamprosate treatment. Serum samples were collected before and after 3 months of acamprosate treatment. Efficacy was defined by self-reported abstinence during acamprosate treatment and average γ -glutamyl transferase (GGT) levels at baseline and 3-month follow-up were used to confirm abstinence. Of those, 14 responders and 18 nonresponders comprised an investigation cohort and an additional 30 responders and 28 nonresponders comprised a replication sample.

Results: Initial metabolite screening was conducted using 32 alcohol-dependent subjects. Glutamate levels were significantly higher at baseline in the 14 responders compared with the 18 nonresponders [$t(30) = 2.7$, $P < 0.05$]. After acamprosate treatment, serum glutamate levels in the responder group significantly decreased compared with baseline [$t(26) = 3.3$, $P < 0.05$]. Similarly, in a replication sample of 58 additional alcohol-dependent subjects, responders had significantly higher glutamate levels at baseline compared with the nonresponder group [$t(88) = 2.8$, $P < 0.05$], which decreased significantly after acamprosate treatment [$t(86) = 3.6$, $P < 0.05$].

Conclusion: Our findings suggest that high glutamate levels may be a biomarker to predict the efficacy of acamprosate treatment in alcohol-dependent subjects.

Disclosure of Interest: None declared.

PP136—GENETIC POLYMORPHISM OF CYP2D6 SIGNIFICANTLY AFFECTS THE PHARMACOKINETICS OF TOLPERISONE

J. Byeon¹; J.-Y. Lee¹; J.-S. Jeon¹; J.-E. Lee¹; S.H. Kim¹; C.-I. Choi¹; Y.-J. Lee²; J.-W. Bae³; C.-G. Jang¹; and S.-Y. Lee¹

¹Laboratory of Pharmacology, School of Pharmacy, Sungkyunkwan University, Suwon; ²College of Pharmacy, Dankook University, Cheonan; and ³Laboratory of Pharmacology, College of Pharmacy, Keimyung University, Daegu, Korea, Republic Of

Introduction: Tolperisone, a centrally acting muscle relaxant, is used for relieving spasticity of neurological origin and muscle spasm associated with painful locomotor diseases. Tolperisone is mainly metabolized by CYP2D6 and CYP2C19, CYP1A2, and CYP2B6 are also involved in the metabolism of tolperisone. CYP2D6 is responsible for variability of drug response, largely due to genetic polymorphism. Therefore, we investigated the effects of CYP2D6 genetic polymorphism on the pharmacokinetics of tolperisone.

Patients (or Materials) and Methods: Thirty healthy Korean subjects were selected and they were divided into 3 different groups according to CYP2D6 genotype, CYP2D6*wt/*wt (*wt= *1 or *2, $n = 10$), CYP2D6*wt/*10 ($n = 10$) and CYP2D6*10/*10 ($n = 10$). After overnight fasting, each subject received a single 150-mg oral dose of tolperisone. Blood samples were collected up to 12 hours after drug intake, and plasma concentrations of tolperisone were determined by using LC-MS/MS analytical system.

Results: C_{max} and AUC_{inf} of tolperisone in CYP2D6*10/*10 genotype group was significantly higher than those in CYP2D6*wt/*wt group ($P = 0.0007$ and $P = 0.0002$, respectively). Apparent oral clearance (CL/F) of tolperisone in CYP2D6*wt/*10 and CYP2D6*10/*10 group was 64% and 75% lower than that in CYP2D6*wt/*wt group ($P < 0.001$ and $P = 0.0001$, respectively). Among 3 genotypes, differences in $t_{1/2}$ of tolperisone were not statistically significant.

Conclusion: Tolperisone is mainly metabolized by CYP2D6 and CYP2D6 genetic polymorphism has a significant impact on the pharmacokinetics of tolperisone.

Disclosure of Interest: None declared.

PP137—EFFECTS OF THE GENETIC POLYMORPHISMS OF HUMAN MULTIDRUG AND TOXIN EXTRUSION 1 (HIMATE1/SLC47A1) TRANSPORTER ON THE RENAL TUBULAR SECRETION OF N1-METHYLNICOTINAMIDE

R. Ogawa^{*}; T. Mikami; M. Takahashi; and H. Echizen

Department of Pharmacotherapy, Meiji Pharmaceutical University, Tokyo, Japan

Introduction: Human multidrug and toxin extrusion 1 (hMATE1/SLC47A1) transporter may be involved in the active elimination clearance of many cationic drugs in the kidneys. Scarcity of knowledge about endogenous substrates of hMATE1 appears to hinder exploration of the roles of genetic polymorphisms on the functional activity of hMATE1.

Patients (or Materials) and Methods: Fifty-four healthy volunteers (32 males and 22 females; 23 [2] years) underwent 3-hour timed-urine collection and blood drawing at the midpoint. Plasma and urinary levels of N₁-methylnicotinamide (MNA) and creatinine were measured with a liquid chromatography-mass spectrometry system. Renal tubular secretion clearance of MNA ($C_{LTS,MNA}$) was calculated by subtracting the renal clearance of creatinine (a substitution of glomerular filtration rate) from that of MNA. Genetic variants of hMATE1/SLC47A1 and another renal cation transporter, hOCT2/SLC22A2, were genotyped by polymerase chain reaction followed by direct sequencing. The protocol of the present study was