ute to the optimization of its dosing. The aim of this study was to evaluate the influence of genetic and clinical factors on TAC pharmacokinetic variability in stable pediatric renal transplant patients.

Patients (or Materials) and Methods: This study was nested in a previous Prograf® to Advagraf® conversion clinical trial in pediatric patients (Eudra CT: 2009-017600-89). Tacrolimus pharmacokinetic analysis was performed using a noncompartamental analysis. CYP3A5 (*3 rs776746 C>G), ABCB1 (rs1045642 C>T), POR (*28 rs1057868 C>T and rs2868177 A>G) genotypes were determined by RT-PCR using commercial Taqman® assays. The impact of individual genetic variants on TAC AUC=24 (adjusted by administered dose/kg) was evaluated and an additive unweighted genetic score was build. Multivariate linear regression was performed including genetic (genetic score), demographic, and clinical information as independent variables and TAC weight-adjusted apparent oral clearance as dependent variable.

Results: Twenty-one kidney transplant pediatric patients (aged between 4 and 17 years) on stable TAC dose were included (12 males and 9 females). Mean (SD) body weight was 42.85 (15.42) kg. Subjects homozygote for CYP3A5*3 and the carriers of rs1045642, rs1057868, or rs2868177 have higher exposure to TAC than noncarriers (P = 0.05). Genetic score groups was as follows: 0 (Group 1), 1 (Group 2), 2 (Group 3), 3 (Group 4), and 4 (Group 5) genetic variants in CYP3A5, ABCB1, and POR genes. There was an increase in TAC dose/kg adjusted AUC as the number of variants in genetic score increase (tendency P = 0.023) and its value is 288% higher in group 5 compared with group 1. Genetic score, BMI, and concomitant deflazacort use were the only covariates retained in the multivariate regression model that explained 64.4% of weight-adjusted apparent oral clearance total variability. Genetic score, the concomitant deflazacort use and BMI explained 33%, 18%, and 15.4% of the total variability, respectively. Mean absolute error (SD) of the predicted deflazacort use, explain a clinically significant amount of the variability in oral clearance of tacrolimus. Larger studies are needed to evaluate the potential utility of these variables in predictive TAC dosing algorithms.

Disclosure of Interest: None declared.

PP133—PHARMACOGENETICS OF THE HUMAN SEROTONIN TRANSPORTER
K. Münch1; J. Stump2; H. Sticht2; M.F. Fromm1; and O. Zolk1
1Institute of Experimental and Clinical Pharmacology and Toxicology; and 2Institute of Biochemistry, Friedrich-Alexander-Universität Erlangen-Nürnberg, Erlangen, Germany

Introduction: The neurotransmitter serotonin (5-hydroxytryptamine; 5-HT) 5-HT transporters (SERTs) are highly expressed in various organs like the brain and gastrointestinal tract. The SERT is a multi-domain protein consisting of a membrane spanning region, a cytoplasmic N-terminus, a large extracellular loop and a C-terminal tail. V488M is a natural variant of SERT in humans, which is located in the extracellular loop H10 and decreases SERT activity in cell lines and in vivo. A careful literature search was performed in order to highlight the relevance of SERT genetic variation in the context of antidepressant treatment.

Methods: A PubMed search was performed for all studies that assessed the influence of SERT genetic variants on antidepressant efficacy or side effects. Pharmacogenetic studies were included if they demonstrated a clinical association. We specifically focused on nonsynonymous SNPs (nsSNPs; that is, SNPs located in coding regions and resulting in amino acid variation in protein products of genes). The impact of amino acid substitutions caused by nsSNPs in SLC6A4 on the structure and function of SERT was investigated by using 6 different in silico prediction tools. Based on the crystal structure of the bacterial homologue LeuT, a homology model of SERT was performed, and the positions of the amino acid substitutions relative to the proposed substrate binding pocket were identified. A rating scale integrating results from in silico predictions and 3D modeling was applied to extract those nsSNPs with a potentially high impact on the structure and function of SERT. For future in vitro testing in transfected cells, these mutations were inserted in an expression vector by site-directed mutagenesis.

Results: We identified 6 nsSNPs within the SLC6A4 gene with potential effects on protein function. Two of them (H143Y and R144Q) reside nearby the cytoplasmatic pore between helix 2 (H2) and H3, which is involved in substrate binding. In both cases, the mutation results in a charge change and most likely in an altered pore opening of SERT. The third SNP (isoleucine 179 to valine) protrudes into the predicted binding cavity of inhibitor and substrate and therefore may influence substrate–transporter interaction. Another SNP causes the expression of a polar threonine 270 instead of a hydrophobic iso-leucine also projecting into the cytoplasmic pore region. The P339L SNP is expected to destabilize H6, which is involved in substrate and inhibitor binding. The V488M SNP in H10 is close to the extracellular pore and may affect antidepressant binding.

Conclusion: By applying a comprehensive screening approach, we identified 6 naturally occurring nsSNPs that are expected to affect substrate (5-HT) and inhibitor (antidepressant drug) binding to SERT. We generated transiently transfected cell lines expressing the 6 variants. Future experiments will have to demonstrate the effects of these nsSNPs on SERT expression and transport function. Of particular interest is the impact of the variants on the inhibition of SERT by antidepressant drugs.

Disclosure of Interest: None declared.

PP134—ESOMEPRAZOLE USED AS A BOOSTER IN A HIV ULTRARAPID CYP2C19 METABOLIZER TREATED WITH VORICONAZOLE
Y. Bouatou1,2; C.F. Samer; K. Ing Lorenzini; Y. Daali; S. Daou1; M. Fathi; M. Rebsamen; J. Desmeules2; A. Calmy; and M. Escher2
1Nephrology; 2Clinical Pharmacology and Toxicology; 3Division of Infectious Diseases; and 4Department of Laboratory Medicine, University Hospitals of Geneva, Geneva, Switzerland

Introduction: Voriconazole, an antifungal agent, is metabolized by CYP450 2C19 (CYP2C19). CYP2C19 activity is modulated by drug–drug interactions (DDI) and genetic polymorphisms. We report a case of therapeutic use of esomeprazole that “boosted” voriconazole plasma concentrations in a CYP2C19 ultrarapid metabolizer HIV patient treated with a CYP2C19 inducer among her antiretroviral treatment (HAART).

Patients (or Materials) and Methods: A 35-year-old African female was diagnosed with AIDS in May 2012. A duodenal histoplasmosis and cryptococcosis infections were treated from June 2012 with a 3-week regimen of amphotericin B–flucytosine then oral voriconazole 100 mg BID. HAART was initiated (emtricitabine, tenofovir, and raltegravir). Voriconazole doses were increased and given intravenously (4 mg/kg/12 h IV) as she developed a single large intracrani-al mass. Several voriconazole trough concentrations (C0) were measured below the therapeutic range (1.0–4.0 µg/mL). CYP2C19 genotype was tested and came heterozygous for the variant allele CYP2C19*17, which is associated with an ultrarapid phenotype. A treatment with esomeprazole 40 mg BID was started and titrated because of severe epigastralgia (histoplasmoscytosis). Subsequent voriconazole C0 were within the therapeutic range. After the proton pump inhibitor was switched to ranitidine, voriconazole C0 were again infratherapeutic despite an increase in voriconazole doses.
Clinical Therapeutics

Besides several changes in HAART were needed due to resistance or persisting replication. After the last change in HAART (darunavir-ritonavir), voriconazole C0 decreased to 0.25 mg/L (30% decrease). Eventually, ranitidine was replaced by esomeprazole 40 mg IV BID. Three days later, voriconazole C0 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 C0 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 C0 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—PHARMACOMETABOLICOSIS 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. Karpak1
1Pharmacy and Psychiatry; 2Pharmacology; and 1Psychiatry, Mayo Clinic College of Medicine, Rochester, United States

Introduction: Acamprosate, a homo-taurine 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 secretion of hMATE1.

Results: 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. Bae1; C.-G. Jang1; and S.-Y. Lee1
1Laboratory of Pharmacology, School of Pharmacy, Sungkyunkwan University, Suwon; 2College of Pharmacy, Dankook University, Cheonan; and 4Laboratory 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*Ut/*Ut (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: Cmax and AUC0-τ 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 t1/2 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 (hMATE1/SLC47A1) TRANSPORTER ON THE RENAL TUBULAR SECRETION OF N1-METHYLNICOTINAMIDE

R. Ogawa1; 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 (Cmax(SL)) 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