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 noncompartmental analysis. *CYP3A5* (*3 rs776746 C>G), *ABCB1* (rs1045642 C>T), *POR* (*28 rs1057868 C>T and rs2868177 A>G) genotypes were determinate by RT-PCR using commercial Taqman® assays. The impact of individual genetic variants on TAC AUC0–24 (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 weight-adjusted apparent oral clearance was of 32.82% (23.36%).
Conclusion: Genetic score composed by variants in *CYP3A5, ABCB1*, and *POR* genes, along BMI and concomitant 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. Münch[1*]; J. Stump[2]; H. Sticht[2]; M.F. Fromm[1]; and O. Zolk[1]
[1]Institute of Experimental and Clinical Pharmacology and Toxicology; and [2]Institute of Biochemistry, Friedrich-Alexander-Universität Erlangen-Nürnberg, Erlangen, Germany
Introduction: The neurotransmitter serotonin (5-hydroxytryptamine; 5-HT) 5-HT is actively cleared from synaptic spaces by SLC6A4, a high-affinity, Na+-, and Cl--dependent transporter localized in presynaptic neuronal membranes. This brain 5-HT transporter appears to be a principal site of action of many antidepressant drugs including those of the tricyclic, SSRIs, and SSNRIs class. Many patients with depression are drug resistant. We hypothesized that changes in the transporter protein due to coding single nucleotide polymorphisms (SNPs) in *SLC6A4* may affect transporter–drug interactions and thus may contribute to the resistance to antidepressant drug treatment.
Patients (or Materials) and Methods: We screened SNP databases (dbSNP, 1000 Genomes, *ESP*) for natural variants in the human *SLC6A4* gene. 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 isoleucine 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 SNPs 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. Bouatou[1,2*]; C.F. Samer[2]; K. Ing Lorenzini[2]; Y. Daali[2]; S. Daou[3]; M. Fathi[4]; M. Rebsamen[4]; J. Desmeules[2]; A. Calmy[3]; and M. Escher[2]
[1]Nephrology; [2]Clinical Pharmacology and Toxicology; [3]Division of Infectious Diseases; and [4]Department 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 intracranial mass. Several voriconazole trough concentrations (C_0) 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 (histoplasmocytosis). Subsequent voriconazole C_0 were within the therapeutic range. After the proton pump inhibitor was switched to ranitidine, voriconazole C_0 were again infratherapeutic despite an increase in voriconazole doses.