PP149—THE CEIBA COCKTAIL FOR DRUG HYDROXYLATION PHENOTYPING IN HISPANIC POPULATIONS

F. De Andres1; M.E.G. Naranjo1; M. Sosa-Macias2; B.P. Lazalde Ramos1; E. Tarazona-Santos1; A.L. Lerena1,3; and CEIBA Consortium
1CICAB, Clinical Research Centre, Extremadura University Hospital, BADAJOZ, Spain; 2Centro Interdisciplinario de Investigación para el Desarrollo Integral Regional del IPN Unidad Durango, CIDIIR-IPN, Durango; 3Laboratorio de Medicina Molecular, Unidad Académica de Medicina Humana y Ciencias de la Salud, Universidad Autónoma de Zacatecas, Zacatecas, Mexico; and 4Departamento de Biología General, Universidad Federal de Minas Gerais, Belo Horizonte, Brazil

Introduction: Interethnic variability of drug metabolism has been demonstrated across Iberoamerican populations by the CEIBA Consortium. Drug-metabolizing enzymes genotype just predicts actual drug metabolic activity (phenotype) in the cases of poor metabolizers. For example, only 30% of ultrarapid metabolizers can be predicted from genotyping (Llerena et al., 2012). Moreover, according to EMA recommendations, development of phenotyping procedures for drug interactions studies and clinical research recommended (EMA, 2013). Therefore, a novel cocktail approach to measure metabolic activity (metabolic ratios) of the main CYP enzymes in just one experiment is developed and validated to be used in the study of Latin-American populations.

Patients (or Materials) and Methods: Subjects were given low oral doses of 100-mg caffeine, 25-mg losartan, 20-mg omeprazole, and 30-mg dextromethorphan. Blood samples were taken 4 hours after administering the drugs to assay the following metabolic ratios in plasma: CYP1A2 (caffeine/paraxanthine), CYP2C9 (losartan/poseidon), CYP2C19 (omeprazole/5-hydroxyomeprazole), CYP2D6 (dextromethorphan/dextorphan), and CYP3A4 (dextromethorphan/3-methylxymorphinan). Solid phase extraction was utilized for analyte extraction and LC-MS/MS to quantify the probe drugs and metabolites.

Results: Recovery values >80% were obtained for all analytes, and no carryover or relative matrix effects were observed. The analytes were separated and detected in 9 minutes and the method was fully validated, with lower limits of quantification ranging from 0.3 ng mL–1 for 5-hydroxyomeprazole to 3.2 ng mL–1 for paraxanthine. The correlation coefficient (r2) values obtained were over 0.995 for all analytes. According to the EMA guideline on bioanalytical method validation, precision and accuracy values below 15% were achieved.

Conclusion: The method was proven to be useful to measure targeted analytes for the evaluation of CYPs hydroxylation capacity in just a single experiment.

Funding Sources: Supported by AEXCID-Cooperación Extremena de Junta de Extremadura (111A002) to Sociedad Ibero-Americana de Farmacogenética-SIFF, and coordinated by the RIBEF network (Red Iberoamericana de Farmacogenética y Farmacogenómica; www.ribef.com).

Disclosure of Interest: None declared.

PP151—PREVALENCE OF CARRIAGE CYP2C9, VKORC1 AND CYP4F2 PolYMORPHISMS IN RUSSIAN PATIENTS WITH HIGH THROMBOTIC RISK PRESCRIBED WARFARIN COMPARED WITH OTHER ETHNIC GROUPS

D. Ivashchenko1; D. Sychev2; L. Rusin1; A. Grachev2; and T. Beloshchikaya1
1Clinical Pharmacology, I.M. Sechenov First Moscow State Medical University; 2Cardiology; and 3Medical Genetic, SM-Clinic, Moscow, Russian Federation

Introduction: VKORC1, CYP2C9, and CYP4F2 responsible for the metabolism of warfarin. Personal and ethnic differences in the genetic profile reveals in determining the outcome of a drug therapy. Aim: to explore the frequencies of CYP2C9, VKORC1, and CYP4F2 genotypes in Russians, compare results with ones for other nations.

Patients (or Materials) and Methods: A total 91 Caucasian subjects were recruited into the study. Forty (48.2%) patients were male and age was 66.17 (10.9) years. All patients had indications to receive warfarin. Medical records for the patients group were reviewed for the relevant clinical data. 5 ml of blood was taken from each subject, and DNA was isolated and used for identification of the CYP2C9 allele *1, *2, *3; G-1639A VKORC1; CYP4F2 V433M rs2108622 C>T using real-time polymerase chain reaction-restriction fragment length polymorphism assay. Results were compared with other ethnic groups and statistically analyzed with chi-square test.

Results: We described the prevalence of CYP2C9 polymorphisms *1/*1 (67%), *1/*2 (9,9%), *1/*3 (11%), *2/*2 (2,2%), *2/*3 (8,8%), same for VKORC1 GG (49,5%), GA (28.6%), AA (22,%) and CYP4F2 CC (57,1%), CT (34,1%), TT (7,7%). No significant deviations from Hardy-Weinberg equilibrium were observed (p < 0.05). Polymorphisms’ frequency of CYP2C9 (P < 0.001) and VKORC1 GG, AA (P < 0.05) in Russian distinguish from Asian. There are no significant interethnic variations for CYP4F2 between Russian, Asian and Caucasian (P > 0.05).

Conclusion: Prevalence of carriage of CYP2C9, VKORC1 polymorphisms in Russian patients with high thrombotic risk is closed to Caucasians and distinguish from Asians but no for CYP4F2.

Disclosure of Interest: None declared.

PP152—TENDENCY TO HIGHER ACTIVITY OF CYP3A5 IN WOMEN WITH STILLBIRTH

K. Zagorodnikova1; M. Kondrahina2; J. Rustanovich; and D. Kostyuchek
1Clinical Pharmacology, I.M. Sechenov First Moscow State Medical University n.a.I.I.Mechnikov, St Petersburg, Russian Federation

Introduction: CYP3A5 is an enzyme known to be involved in metabolism of human hormones – progesterone and testosterone, which metabolism may play a role in either disease origin or treatment efficacy in women with stillbirth. There is a common genetic polymorphism leading to its increased activity (6986G). Our aim was to investigate possible role of this polymorphism in stillbirth.

Patients (or Materials) and Methods: All women admitted to gynecology department of university clinics with verified diagnoses of stillbirth were considered for recruitment to the study. At the same time women who attended routine pregnancy registration were screened and recruited at the same time as the study group being matched by their age and concomitant diseases. All women who gave informed consent were recruited. Peripheral venous blood samples were drawn into EDTA tubes. DNA was extracted. Polymerase chain reaction in real time was performed to detect genetic variants of CYP3A5 *3/*1 (6986G). Chi-square test was used for frequency comparisons using statistical software Graphpad Prism 5.0.

Results: Fifty-three women with stillbirth were recruited to the study. Control group consisted of 92 matched women. Frequency of the minor