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IS PHARMACOKINETICS OF STIRIPENTOL LINEAR? E. Rey, PharmD, V. Jullien, PharmD, P. D'Athis, PhD, J. Vincent, PharmD, G. Pons, MD, PhD, Hopital Saint Vincent de Paul, Centre Universitaire de Dijon, Biocodex, Paris, France.

BACKGROUND: Stiripentol (STP) is an antiepileptic drug which efficacy has been demonstrated in severe myoclonic epilepsy and strongly suggested in partial epilepsy as an add-on therapy. A pharmacokinetic (PK) study was performed in healthy volunteers as the linearity of STP PK remains controversial.

METHODS: A randomised double blind cross-over study at 3 different single oral doses (500, 1000, 2000 mg as tablets) was performed in 12 subjects. Sixteen blood samples were collected in each subject. STP plasma concentrations were determined by HPLC. Data were analysed using a compartmental analysis.

RESULTS: A two-compartment model with a zero order absorption (R0) and a significant lag-time fitted the data. The following parameters were calculated : Cmax (3.1±0.9, 7.1±1.9,13.2±3.6 mg/l), R0 (356±194,742±634, 871±362 mg/h), Cl/F (58±28, 33±10, 25±8 l/h), AUC 0-inf (9.3±3.4, 33.1±10.9, 87.6±27.7 mg.h/l) and $T1/2_{\beta}$ (4.4±2.1, 10.1±3.3, 13.7±6.2 h) after the 500, 1000 and 2000 mg dosages respectively. Dose-normalized Log_{10} (AUC) were found significantly different ($p < 10^{-10}$, ANOVA) between groups. However the half-life was not significantly different between the 1000 and the 2000 mg dosage.

CONCLUSION: A dose-dependent non-linear STP PK can be concluded, probably due to an increase in bioavailability , possibly a saturable first-pass effect. However stable concentrations are expected at steady-state as the elimination phase is linear (first order).

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PHARMACOGENETIC PROFILING OF DRUG METABOLIZING ENZYME GENES. P. H. Hendolin, PhD, J. Blievernicht, E. Schaeffeler, U. Ristonmaa, A. Liikola, P. Kolu, K. Klein, J. Aalto, U. Zanger, V. Korhonen, Dr. Margarete Fischer-Bosch-Institut für Klinische Pharmakologie, Stuttgart, Germany, Oy Jurilab Ltd, Kuopio, Finland.

BACKGROUND: Pharmacogenetic testing has become increasingly important in drug development and pharmaco-vigilance processes. To understand the inter-individual differences in active pathways, tests that target multiple drug metabolizing and drug interacting proteins are required.

METHOD: A DNA microarray was developed that consists of an array-of arrays for genotyping 16 samples simultaneously (the DrugMEt™ Test). Genotyping is accomplished in a single reaction with allele-specific primers for 27 SNPs of eight highly polymorphic genes: *CYP2B6, CYP2C9, CYP2C19, CYP2D6, CYP3A5, TPMT, NAT2,* and *MDR1*. The accuracy and reproducibility were evaluated, and a method comparison with the TaqMan™ assay was performed. The applicability of the method was investigated with samples from different ethnic backgrounds.

RESULTS: For the various SNPs, an accuracy >99%, and reproducibility of >95%, was observed. The method comparison indicated >95% concordance between the DrugMEt™ Test and TaqMan™ assay. The genotype frequencies of the Caucasian, African American, and Asian populations matched those published in the literature.

CONCLUSIONS: The multigene DrugMEt™ microarray provides a straight-forward basis for the selection of a drug compound for future development, and identification of the potential responder population. Moreover, drug-interacting pathways may be identified.

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MULTIPLE OATP TRANSPORTERS MEDIATE THE CELLULAR UPTAKE OF ROSUVASTATIN. R. H. Ho, MD, Y. Wang, PhD, B. F. Leake, BS, R. B. Kim, MD, Vanderbilt Univ. Medical Center, AstraZeneca, Nashville, TN.

Rosuvastatin is an HMG-CoA reductase inhibitor (statin) used in the treatment of hypercholesterolemia. Rosuvastatin is not subject to significant metabolism; therefore its disposition is thought to be highly dependent on drug transporters expressed in organs such as the intestine, liver, and kidney. Recent studies have shown that OATP1B1 (OATP-C) can mediate the hepatic uptake of this drug. However, the extent and relevance of other OATP transporters to the disposition of this drug has not been clarified. In this study, we expressed an array of human and rat Organic Anion Transporting Polypeptide (OATP) transporters using a recombinant vaccinia system. As expected, we are able to confirm that human OATP1B1 is able to mediate the cellular uptake of rosuvastatin. In addition, human OATP1A2 (OATP-A), OATP2B1 (OATP-B), OATP1B3 (OATP-8), as well as rat Oatp1a1 (Oatp1), Oatp1a4 (Oatp2), Oatp1a5 (Oatp3), and Oatp1b2 (Oatp4) were also capable of rosuvastatin uptake. When we expressed allelic variants of human OATP1B1, profound loss of rosuvastatin uptake was noted in cells expressing *5, *9, *15, and *16 (*1b+*9) variants. Accordingly, our findings would suggest multiple OATP transporters mediate the uptake of rosuvastatin from the GI tract and liver. Moreover, involvement of other hepatic OATP transporters is likely to attenuate the impact of *SLCO1B1* (*OATP-C*) SNPs to the overall disposition of rosuvastatin *in vivo*.

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HAPLOTYPE STRUCTURES OF CYCLOOXYGENASE GENES IN HUMAN ETHNIC POPULATIONS. H. Kim, DDS, PhD, R. A. Dionne, DDS, PhD, NIDCR/NIH, Bethesda, MD.

BACKGROUND: In spite of the critical role of the COX genes in inflammation, influence of their genetic variation on pain has not been clearly elucidated. The haplotype, a particular combination of alleles observed in populations, focuses on patterns of a few single nucleotide polymorphisms (SNPs) that define each haplotype and has recently contributed to the identification of genes for disorders that are common but complex in inheritance.

METHODS: Normal subjects (426 females and 285 males) from 4 major ethnic populations were genotyped for genes encoding COX-1 (N= 5 SNPs) and COX-2 (N= 9 SNPs). For genotyping of genomic DNA, 5' exonuclease allelic discrimination assay with the ABI Prism 7900 Sequence Detection System was used. The haploblocks based on four gamete rules were generated by Haploview version 2.05 with SNPs whose minor allele frequency > 0.1, genotype success rate > 0.9 and P > 0.05 in the Hardy-Weinberg equilibrium (HWE) test.

RESULTS: In the present human cohort, ethnic populations showed differences in HWE, haploblocks and haplotype tag SNPs (htSNPs) from COX-1 and COX-2 genes. Two SNPs from COX-1 gene and COX-2 gene are out of HWE in Asian Americans while 2 SNPs from COX-2 gene are out of HWE in other ethnic populations. One or two haploblocks were found in COX genes with 3 to 7 htSNPs.

CONCLUSIONS: Our observation provides basic ethnic background information for analysis of genetic effects of COX-1 and COX-2 genes on individual variance in pain sensitivity and responses to drugs.