PI-48

RISK OF UNDERTREATMENT WITH THE STANDARD ABACAVIR 300 MG DOSE. V. Jullien, PharmD, S. Urien, MD, PhD, J. Dimet, PharmD, E. Rey, PharmD, N. Dupin, MD, D. Salmon, MD, PhD, G. Pons, MD, PhD, J. Treluyer, MD, PhD, Hôpital Saint-Vincent de Paul, Hôpital René Huguenin, Hôpital Cochin, Paris, France.

Purpose: To study the relevance of the current 300 mg B.I.D. abacavir dose for H.I.V.-infected adults.

Methods: Abacavir plasma concentrations were obtained from therapeutic drug monitoring results. Population pharmacokinetic analysis was performed using a nonlinear mixed effects modeling method.

Results: Abacavir concentration-time profiles were best described by a one-compartment open-model with linear absorption and elimination. Typical values of absorption rate constant, apparent distribution volume and apparent plasma clearance (CL/F) were 3.3 h^{-1}, 98 L and 48 L/h respectively. CL/F was positively related to BW. A risk of undertreatment as a function of BW was identified as the percentage of patients reaching the area under the curve value providing the optimal antiviral efficacy decreased from 94 to 22 % when BW increased from 36 to 102 kg.

Conclusion: This study identified BW as a major determinant of abacavir clearance. These results suggest the administration of larger doses to high BW patients.

PI-49

EFFECT OF BETA-1 ADRENERGIC RECEPTOR POLYMORPHISMS ON THE TOLERABILITY OF METOPROLOL CR/XL IN HEART FAILURE. S. G. Terra, PharmD, D. F. Pauly, MD, PhD, C. R. Lee, PharmD, J. Patterson, PharmD, K. F. Adams, Jr, MD, R. S. Schofield, MD, K. K. Hamilton, MD, J. A. Hill, MD, J. M. Aranda, MD, J. A. Johnson, PharmD, University of Florida, University of North Carolina, Gainesville, FL.

β_1-adrenergic receptor (β_1AR) polymorphisms at codons (c) 49 (Ser49Gly) and 389 (Arg389Gly) have functional effects and have been associated with the blood pressure lowering effect of β-blockers. We hypothesized that these polymorphisms would be associated with differences in initial tolerability of β-blocker therapy in heart failure (HF) patients. We prospectively enrolled 60 β-blocker naïve patients with NYHA II-III systolic HF. Patients were initiated on metoprolol CR/XL (MXL) 12.5-25 mg and titrated q 2 weeks (as tolerated) to 200 mg/day or maximum tolerated dose over 8 weeks. Tolerability to MXL was assessed by the Minnesota Living with HF questionnaire (MLWHF), 6-minute walk distance (6-min WD), and final MXL dose. Decompensation was defined as death, HF hospitalization, increase in other HF meds, or need to discontinue MXL over a 6-month period. Response data by c389 revealed no significant differences across genotype in any measure (Table). At baseline, Gly49 carriers demonstrated lower 6-min WD compared to Ser49Ser (346 meters vs. 296 meters, p=0.06). There were no significant differences in end of study response by c49 genotype; decompensated HF occurred in 35% of Ser49Ser patients and 29% of Gly49 carriers. In conclusion, the c49 and 389 polymorphisms of the β_1AR do not appear to be associated with the initial tolerability of β-blockers in HF patients.

Response Stratified by c389 Genotype (mean ± SE, unless noted)

	Arg389Arg; n = 28		Gly 389 Carriers; n = 32		P*
	Baseline	Final	Baseline	Final	
Decompensation, n(%)		7 (25%)		13 (40%)	0.27
6-min WD (meters)	330 ± 21	357 ± 27	298 ± 13	302 ± 18	0.09
MLWHF	28 ± 4	21 ± 4	37 ± 4	31 ± 3	0.10
HR (bpm)	80 ± 2	64 ± 2	79 ± 1	70 ± 2	0.10
SBP (mm Hg)	120 ± 3	110 ± 4	119 ± 3	110 ± 3	0.97
MXL Dose (mg/day)		119 ± 13		100 ± 13	0.34

*Final comparison.

PI-50

PHARMACOGENETICS OF CYP2C8 AND HAPLOTYPIC ASSOCIATIONS IN THREE DISTINCT ASIAN POPULATIONS. C. Kibat, B.Sc, Q. Zhou, PhD, H. Li, PhD, B. Chowbay, PhD, Clinical Pharmacology Lab, National Cancer Centre, Singapore.

CYP2C8 is a polymorphic enzyme involved in the metabolism of several clinically important drugs, e.g. paclitaxel, all-*trans* retinoic acid and cerivastatin. The aim of the present study was to determine and compare allele frequencies of reported SNPs in the *CYP2C8* gene among three distinct Asian populations and to investigate haplotypic associations among the SNPs. Seventeen SNPs were analysed: 3 in the 5′ UTR, 7 in the coding region, 6 in the intronic region, and 1 in the 3′UTR in a total of 280 healthy subjects (100 Chinese, 90 Malays and 90 Indians) using PCR-RFLP and direct DNA sequencing. The distribution of allelic frequencies were high in the 5′UTR in all 3 ethnic groups (-411C>T, range: 0.61-0.79; -370T>G, range: 0.23-0.33; -271C>A, range:0.10-0.16). Similarly, interethnic difference in allelic frequencies were noted for the following intronic SNPs: IVS2-64A>G, range: 0.40-0.60; IVS2-13Tins, range:0.34-0.36, IVS7+49T>A, range: 0.43-0.66. The seven cSNPs (416G>A, 805A>T, 792C>G,1169T>C, 1196A>G, 1210C>G, 1230C>T and 1232A>T) and 3 intronic SNPs (IVS1 –37C>T, IVS2 –36G>A and IVS8 –92G>A) were very rare in all 3 ethnic groups. Marked interethnic variations in allele frequencies were apparent at 5′UTR (-411T>C), intron 2 (IVS2 -64A>G) and intron 7 (IVS7 +49T>C) ($P<0.05$). Haplotype analysis revealed 8 hyplotypes in the Chinese, 8 in the Malays and 12 in the Indians. Future studies should aim to investigate the functional consequences of these haplotypic associations and their impact on the pharmacokinetics of CYP2C8 substrates.

PI-51

FUNCTIONAL CHARACTERIZATION OF MDR3 PROMOTER MUTATIONS DETECTED IN INTRAHEPATIC CHOLESTASIS OF PREGNANCY. C. Pauli-Magnus, MD, T. Lang, PhD, D. Jung, PhD, G. A. Kullak-Ublick, MD, P. J. Meier, MD, University Hospital Zurich, Epidauros AG, University Zurich, Zürich, Switzerland.

Background: Intrahepatic cholestasis of pregnancy (ICP) is a liver disorder associated with risk of intrauterine fetal death and prematurity. There is increasing evidence that genetically determined dysfunction in the canalicular ABC transporter MDR3 (multidrug resistance protein 3) is a risk factor for ICP. The aim of this study was to functionally characterize newly detected MDR3 promoter variants in ICP patients.

Methods: Luciferase reporter constructs of the human MDR3 5‘-regulatory regions were generated by PCR and ligated into the pGL3-Basic vector. DNA from three different ICP patients (covering the wildtype sequence and eight promoter mutations, three of which were ICP-specific: intron -4: C(-10)T; exon-3: A(-358)G; intron-3: C(-31)T) was used. The human hepatocyte derived cell lines Huh7 and HepG2 were transiently transfected with reporter constructs to assay for promoter activity.

Results: In both cell lines, no differences in promoter activity of the mutated constructs were observed with respect to the promoter containing the reference sequence. In HepG2 cells, activity of the two mutated constructs amounted to 96% and 103% of reference activity, respectively. In Huh-7 cells activity were 90% and 85% of reference activity, respectively.

Conclusion: Results indicate that the tested promoter mutations do not change the activity of the MDR3-promoter. They therefore do not seem to play a pathophysiological role in ICP development.