PI-55

EFFECTS OF COMBINED CYP2C9 AND 2C19 POLYMORPHISM ON THE PHARMACOKINETICS OF GLIBENCLAMIDE IN CHINESE SUBJECTS. O. Q. Yin, PhD, B. Tomlinson, M. S. Chow, The Chinese University of Hong Kong, Shatin, Hong Kong.

BACKGROUND: Recent in vitro studies showed that both CYP2C9 and 2C19 contributed to the metabolism of gliphenclamide (glyburide). This study investigates the relative in vivo contribution of these enzymes to glibenclamide pharmacokinetics.

METHODS: Eighteen healthy male Chinese subjects were divided into 3 groups: CYP2C9 EM/CYP2C9*1/*1 (group 1, n=6), CYP2C9 PM/CYP2C9*1/*1 (group 2, n=6), and CYP2C9 EM/CYP2C9*1/*3 (group 3, n=6). Subject received a single oral dose of 5 mg glibenclamide, and multiple blood samples were collected over 12 h.

RESULTS: No significant differences in glibenclamide pharmacokinetics were observed between CYP2C9 EM and PM subjects (group 1 vs 2). However, the plasma glibenclamide concentration was significantly higher in CYP2C9*1/*3 than CYP2C9*1/*1 subjects regardless of CYP2C9 genotype (group 3 vs 1 or 2), and their respective AUC0-24 were 1.03±0.50, 0.46±0.13 and 0.57±0.11 μg·h/mL (ANOVA, p<0.05), and respective t1/2 were 3.58±1.25, 2.09±0.22 and 2.2±0.27 h (ANOVA p<0.05). In addition, 50% of CYP2C9*1/*3 subjects and 17% of CYP2C9*1/*1 subjects developed blood glucose levels below 3 mmol/L and required oral glucose administration.

CONCLUSION: CYP2C9 but not 2C19 polymorphism appears to exert dominant influence on glibenclamide metabolism. In CYP2C9*1/*3 heterozygote subjects, the pharmacokinetics and pharmacodynamics of glibenclamide were markedly changed, and the glibenclamide dosage may need to be adjusted to reduce the risk of hypoglycemia.

PI-56

CYP2C19 GENOTYPE PREDICTS DURATION OF RESPONSE TO TAMOXIFEN IN ADVANCED BREAST CANCER. R. van Schaik, PhD, E. Teuling, M. Meijer, I. van der Heiden, M. van Fessel, M. van Vliet, I. van Staveren, M. Look, J. Klijn, PhD, MD, J. Fockens, PhD, J. Lindemans, PhD, E. Berns, PhD, Erasmus University Medical Center, Rotterdam, The Netherlands.

BACKGROUND: Resistance to anti-estrogens is a major problem in breast cancer treatment. The anti-estrogen tamoxifen is metabolized by cytochrome P450 enzymes. Genetic polymorphisms in these enzymes may alter tamoxifen metabolism and determine response to therapy.

METHODS: Genomic DNA from 248 retrospectively collected estrogen receptor positive primary breast tumor specimens from patients with advanced disease were analysed for CYP2D6, 2B6, 2C9, 2C19 and 3A5 variant alleles. Results were compared to patient and tumor characteristics, outcome of response and time to tumor progression.

RESULTS: No relation between patient or tumor characteristics and CYP450 genotype was observed, nor did CYP3A5, 2B6, 2C9 or 2D6 genotype correlate with treatment outcome. However, the CYP2C19*1/*1 genotype was significantly associated with a shorter time to tumor progression (hazard ratio 0.64; 95% CI. 0.47–0.87; p=0.004).

CONCLUSIONS: Our data suggest that the duration of response to tamoxifen therapy is dependent on CYP2C19 genotype. Further studies are needed to investigate whether inhibition of CYP2C19 activity may result in a longer response to tamoxifen.

PI-57

HEPATOCELLULAR NUCLEAR FACTORS (HNF) 4a AND 1α SYNERGISTICALLY UP-REGULATE CAR-MEDIATED TRANSCRIPTIONAL ACTIVITY OF HUMAN CYP2C9 GENE. H. G. Xie, MD, PhD, W. Lee, PhD, C. Yu, PhD, C. M. Stein, MD, R. B. Kim, MD, Vanderbilt University School of Medicine, Nashville, TN.

BACKGROUND: There are two CAR response elements, −1783/−1856 bp and −2899/−2883 bp, in the −3 kb CYP2C9 promoter region. The proximal element is thought to mediate PXR response while the distal one may have a CAR effect. HNFs are important co-agonists of gene expression. The aim of this study was to define the roles of HNF4a and HNF1α in CAR-mediated transactivation of human CYP2C9 gene.

METHODS AND RESULTS: Three CYP2C9-luciferase reporter constructs (−3kb, −2kb, −1kb) were transfected into HepG2 cells. Co-transfection with CAR, HNF4a, and HNF1α alone did not significantly change their luciferase activities (LA). For the −3kb and −2kb constructs, compared with CAR alone, CAR co-transfection with HNF4a increased LA 3.9-fold and 2.9-fold (P <0.001, and P <0.01), respectively. For the −1kb construct, no significant differences were observed when CAR alone or CAR was co-transfected with HNF4a or HNF1α. Similarly, for the −2kb construct, HNF4a increased mouse CAR-mediated LA 2.6-fold (P <0.05) but HNF1α had a smaller effect.

CONCLUSIONS: These data suggest that HNF4a, and to a lesser extent HNF1α, synergistically up-regulate CAR-mediated transcriptional activity of CYP2C9 gene, and that there is a CAR-response element between −1kb and −2kb of CYP2C9 promoter region as previously noted.

PI-58

HUMAN SULFOTRANSFERASE (SULT) 1A3 PHARMACOGENETICS: GENE DUPLICATION AND FUNCTIONAL GENOMICS. M. Hildebrand, BS, O. Salavaggione, MD, Y. Martin, BS, H. Flynn, BS, S. Jalal, PhD, E. Wieben, PhD, R. Weinshilboum, MD, Mayo Clinic, Rochester, MN.

BACKGROUND/AIMS: SULT1A3 catalyzes the sulfate conjugation of catecholamines and structurally related drugs. Following completion of the Human Genome Project, it appeared that SULT1A3 might be duplicated. The purpose of this study was to verify and characterize this gene duplication.

METHODS: PCR-based assays and FISH were used to verify that 2 SULT1A3 genes are present on chromosome 16. Reanalysis of previous gene resequencing data was performed to confirm the presence of SULT1A3 SNPs previously and also to identify novel polymorphisms. Functional genomic studies were performed on 3 novel cSNPs to determine levels of SULT1A3 activity enzyme activity, immunoreactive protein and substrate kinetics. RT-PCR was used to determine if both SULT1A3 copies are transcriptionally active.

RESULTS: Two copies of SULT1A3 are present on chromosome 16. All previously reported SNPs were confirmed, and 11 novel SNPs were identified. Both genes can produce mRNA transcripts and functional genomic studies showed that 2 novel cSNPs resulted in decreased activity and levels of protein.

CONCLUSIONS: The duplication of SULT1A3 will have to be taken into account during future efforts to understand individual variation in SULT1A3 activity or properties.