

699G>A (Met233Ile) loci. Genotyping was performed using PCR-RFLP based methods or by direct nucleotide sequencing. Pharmacokinetic parameters for docetaxel were estimated using non-compartmental analysis. The relationships between variant genotypes and pharmacokinetic parameter estimates were evaluated with a non-parametric Kruskal-Wallis test.

RESULTS: Only OATP1B3 was capable of transporting docetaxel to a significant extent ($P = 0.04$), suggesting that this solute carrier is responsible, at least in part, for hepatocellular drug uptake. The observed frequencies for the *CYP3A5*3C*, *ABCB1* 1236T, 2677T, 2677A, 3435T, *SLCO1B3* 334G and 699A alleles were 83.9%, 50.5%, 37.4%, 6.1%, 42.9%, 81.9%, and 81.5%, respectively, and all were in Hardy-Weinberg equilibrium. Significant linkage was observed between SNPs from within the same gene, as predicted previously. The observed mean clearance of docetaxel was 26.6 L/h (individual range, 9.69 to 89.8 L/h). The *CYP3A5* and *ABCB1* genotypes or haplotypes were not statistically significantly associated with the clearance of docetaxel ($P = 0.47$ and $P > 0.16$, respectively). Likewise, no statistically significant association was observed between the *SLCO1B3* variants and any of the studied pharmacokinetic parameters ($P > 0.07$).

CONCLUSION: This study indicates that the presently evaluated variant alleles in the *CYP3A5*, *ABCB1*, and *SLCO1B3* genes do not explain the substantial interindividual variability in docetaxel pharmacokinetics.

OI-C-I

ON THE ROLE OF ABCB1 AND ABCC2 IN DIAPLACENTAL TRANSPORT OF TALINOLOL USING THE DUALY PERFUSED HUMAN PLACENTA MODEL. V. Minarikova, PhD, K. May, K. Linnemann, MD, C. Fusch, MD, W. Siegmund, MD, University of Greifswald, Department of Clinical Pharmacology, University of Greifswald, Pediatric Hospital, Greifswald, Germany.

BACKGROUND: The multidrug resistance-associated protein 2 (ABCC2, MRP2) and P-glycoprotein (ABCB1, P-gp) which are expressed in placental syncytiotrophoblasts are supposed to form a functional barrier between maternal and fetal blood circulation. Therefore, we investigated the influence of the P-gp and MRP2 inhibitor verapamil, the P-gp inhibitor PSC833 and the MRP2 inhibitor probenecid on the materno-fetal transfer of talinolol a substrate of P-gp and MRP2 using the dually perfused human placenta model.

METHODS: 37 term human placentas were obtained after non-complicated vaginal or cesarean delivery and genotyped for ABCB1 and ABCC2. 19 placentas were dually perfused for 5 hours using a well standardized technique. The materno-fetal transfer of talinolol (0.8 μ M) was studied in a controlled, randomized manner without and in presence of verapamil (30 μ M, $n = 6$), PSC833 (1.9 μ M, $n = 6$) and probenecid (10 mM, $n = 6$) the. The transport of talinolol was related to permeability of antipyrine (0.4 mM) and creatinine (1.3 mM) which cross the placenta by non-ionic diffusion. Perfusion volume, glucose consumption and lactat production were measured to supervise viability of the perfused cotyledon.

RESULTS: The permeability of talinolol relative to creatinine permeability was significantly higher in presence of verapamil (0.66 ± 0.16 vs 0.53 ± 0.09 ; $p < 0.03$) and probenecid (0.68 ± 0.13 vs 0.59 ± 0.15 ; $p < 0.03$). There was no effect of PSC833 on the diaplacental transfer of talinolol (0.48 ± 0.11 vs 0.46 ± 0.09 ; $p = 0.35$). We observed a significant correlation between MDR1 mRNA expression and MDR1 genotype in exon 26 at position 3435. In placentas with the homozygous ABCB1 3435TT polymorphism, the ABCB1 mRNA expression was significantly lower than in placentas with the 3435CC wildtype (1.89 ± 1.32 vs 5.36 ± 3.46 ; $p = 0.037$) and heterozygous type 3435CT (1.89 ± 1.32 vs 8.10 ± 12.8 ; $p = 0.035$).

CONCLUSION: MRP2 in contrast to P-gp plays a significant role in diaplacental transport of the β -adrenergic blocker talinolol.

OI-C-II

RISK MANAGEMENT DURING DRUG DEVELOPMENT: PREGNANCY PREVENTION STRATEGIES EMPLOYED IN CLINICAL TRIALS SUBMITTED TO THE FDA. E. Pinnow, P. Scott, J. Derbis, T. Toigo, K. Uhl, FDA, Office of Women's Health (OWH), FDA, Office of Special Health Issues (OSHI), Rockville, MD.

BACKGROUND: The FDA requires clinical trials to include a representative sampling of the population that will likely use the drug. Although women may not be explicitly excluded, restricting inclusion to females of non-childbearing potential (non-CBP) may hinder female participation. These exclusions persist despite the contraceptive requirements that can be imposed for trial participation. The purpose of this study is to describe the contraceptive requirements for women and men participating in pharmacologic clinical trials.

METHOD: The study used an OSHI database that included information on trial phase and inclusion by gender. Eight-hundred-eighty-three new commercial drug protocols submitted to the Center for Drug Evaluation and Research, between January 1–April 30, 2002 were identified. A subset of 711 protocols for non-sex specific indications was reviewed by Office of Women's Health to abstract information on contraception requirements.

RESULTS: One-hundred-twelve (15.8%) protocols excluded females of childbearing potential (FCBP). FCBP were excluded in 24.6% of phase 1, 13.5% of phase 2, 4.7% of phase 3 and 10.3% of phase 4 trials. Of 112 protocols that excluded FCBP, 38 included only males, 18 included only females (all non-CBP), 56 included males and females of non-CBP, and 599 included both males and females. Of the 599 protocols that included both sexes, contraception for female participants was required in 554 (92%) and in 74 (12%) for male participants. Of the protocols with a contraception requirement for women, 197 contained vague language (e.g. "acceptable", "effective" or "adequate" contraception) and 357 contained a list of acceptable method(s). Of the 357 protocols, 311 required one or more approved contraception method and 46 required at least two combined methods of contraception.

CONCLUSION: Contraception for women is generally required for participation in drug trials. It is routinely imposed at all trial phases and may involve more than one method. Men of reproductive age are less likely to have similar restrictions. Inadequate participation of females of child-bearing potential is an important risk management issue. Broad patient representation in clinical trials is essential to ensure the safety and efficacy of FDA regulated products in diverse populations.

OI-C-III

EXAMINATION OF ACETAMINOPHEN PROTEIN ADDUCTS (APAP-CYS) IN CHILDREN AND ADOLESCENTS WITH ACETAMINOPHEN OVERDOSE. L. P. James, MD, P. M. Simpson, PhD, L. Letzig, BS, G. L. Kearns, PharmD, PhD, J. A. Hinson, PhD, Arkansas Children's Hospital Research Institute and University of Arkansas for Medical Sciences, Children's Mercy Hospital, University of Arkansas for Medical Sciences, Little Rock, AR.

BACKGROUND: We previously reported that measurement of acetaminophen (APAP) protein adducts by an HPLC-EC assay was a sensitive and specific measure of APAP-related acute liver failure (ALF) in children.

METHOD: Relationships between adducts (APAP-CYS) and clinical/laboratory parameters in 75 children and adolescents ($n = 75$; median age 13.3 years; range 0–17 years; 58 females) with APAP overdose were examined. Serum samples were obtained by convenience sampling during the time of routine clinical monitoring for APAP overdose and APAP-CYS was measured by HPLC-EC. The diagnosis of APAP overdose was determined by history of toxic dosing (>150 mg/kg APAP) or elevated serum APAP levels at admission. Management of the overdose was determined by the treating physician. The severity of APAP toxicity was stratified as none to

mild—peak AST < 100 IU/L; moderate—peak AST 100–1000 IU/L; severe—peak AST > 1000 IU/L). For subjects with more than one sample available for analysis, the peak APAP-CYS value was used for comparison to other parameters.

RESULTS: 71 patients had acute single ingestions of APAP (median reported dose 272 mg/kg), while 4 had chronic ingestions. One subject required a liver transplant, while all others had spontaneous recovery. All but one subject received treatment with N-acetylcysteine. 40 subjects had no to mild; 16 had moderate and 19 had severe toxicity. APAP-CYS was detected in all 207 samples. Peak APAP-CYS (median [range] nmol APAP-CYS/mL serum) was higher in subjects with severe toxicity (2.53 [0.44–23.91]) compared to those with moderate toxicity (0.35 [0.09–2.14]; $p = 0.0001$) and peak APAP-CYS was higher in those with moderate toxicity compared to those with no to mild toxicity (0.24 [0.04–1.22]; $p = 0.016$). For subjects in whom the time of the overdose was known ($n = 52$), APAP-CYS was higher in those at risk for toxicity (Rumack nomogram; $n = 44$), compared to those at no risk ($n = 8$; $p = 0.008$). Peak APAP-CYS did not correlate with prolongations of prothrombin time. Peak APAP-CYS was also compared to peak values for interleukin (IL)6, IL8, IL10 and monocyte chemoattractant protein 1 (MCP-1). Peak APAP-CYS was higher in patients with an elevated MCP-1 level ($p = 0.008$).

CONCLUSION: APAP-CYS levels in serum correlate with the severity of liver injury in children and adolescents with APAP overdose.

OI-C-IV

A DRUG BURDEN INDEX TO DEFINE THE FUNCTIONAL BURDEN OF MEDICATIONS IN OLDER PEOPLE. S. N. Hilmer, MD, PhD, D. E. Mager, PharmD, PhD, E. M. Simonsick, PhD, Y. Cao, MB, S. M. Ling, MD, B. G. Windham, MD, T. B. Harris, MD, MS, J. T. Hanlon, PharmD, MS, S. M. Rubin, MPH, R. I. Shorr, MD, MS, D. C. Bauer, MD, MPH, D. R. Abernethy, MD, PhD, University of Sydney, University at Buffalo, SUNY, National Institute on Aging, Johns Hopkins Medicine, University of Pittsburgh, University of California, San Francisco, University of Tennessee, Memphis, Sydney, Australia.

BACKGROUND/AIMS: Older people carry a high burden of illness for which medications are indicated along with increased risk of adverse drug reactions. We developed an index to determine drug burden based on pharmacological principles of anticholinergic and sedative drugs and evaluated the relationship of this index to physical and cognitive performance apart from disease indication and relative to simple counts of specific and total drugs concurrently taken.

METHODS: Data from the Health, Aging and Body Composition (Health ABC) study on 3075 well functioning community dwelling persons aged 70–79 were used to assess the cross-sectional association of drug burden index score with a validated composite continuous measure of physical function with scores ranging for 0 to 4, and cognitive performance with the Digit-Symbol Substitution Test (DSST). For both measures, higher values indicate better function. Associations were evaluated using multiple linear regression.

RESULTS: Use of anticholinergic and sedative medications was associated with poorer physical performance score: (anticholinergic exposure [2.08 vs 2.21, $p < 0.0001$]; sedative exposure [2.09 vs 2.19, $p < 0.0001$]) and cognitive performance shown by DSST score (anticholinergic exposure [34.5 vs 35.5, $p < 0.05$]; sedative exposure [34.0 vs 35.5, $p < 0.05$]). Associations were strengthened when pharmacological principles of dose exposure and response were used to calculate exposure with an increase of one unit in the drug burden index associated a deficit of 0.15 points ($p < 0.0001$) on the physical function scale and 1.5 points ($p < 0.01$) on the DSST. These values were three to four times of that associated with a single comorbid illness.

CONCLUSION: Use of the drug burden index indicates that anticholinergic and sedative drug exposure is associated with poorer

functional status in community-dwelling older people. This pharmacologically based approach provides a useful evidence-based tool for assessing the functional impact of exposure to medications in this population.

OI-D-I

A NOVEL GENOME-WIDE APPROACH TO IDENTIFY GENETIC VARIANT THAT CONTRIBUTE TO CHEMOTHERAPY-INDUCED CYTOTOXICITY. R. S. Huang, PhD, S. Duan, PhD, W. K. Bleibel, E. O. Kistner, PhD, T. A. Clark, T. X. Chen, A. C. Schweitzer, J. E. Blume, M. E. Dolan, PhD, University of Chicago, Affymetrix Inc., Chicago, IL.

BACKGROUND/AIMS: The polygenic nature of the sensitivity to drugs has limited the success of candidate gene approaches. We present a novel genome-wide model utilizing human lymphoblastoid cell lines from the International HapMap consortium, of which extensive genotype information is available, to identify genetic variants that contribute to chemotherapeutic agents-induced toxicity.

METHODS: Our model was based on molecular biology, integrated genotype, gene expression and phenotype as measured by sensitivity of HapMap cell lines to chemotherapeutic drug. Cell lines derived from 30 trios of European descent (CEU) and 30 trios of African descent (YRI) were utilized. Cell growth inhibition with increasing concentrations of etoposide for 72 h was determined using alamarBlue[®] assay. Gene expression in these 180 cell lines was determined using the Affymetrix GeneChip[®] Human exon 1.0 ST Array. SNP genotypes and etoposide IC₅₀ were linked through whole genome association in cell lines from combined and independent CEU and YRI populations. A second association test was performed between SNP genotype and gene expression and linear regression was utilized to evaluate the correlation between gene expression and etoposide IC₅₀.

RESULTS: Among the 387,417 SNPs tested, 49, 122 and 51 SNPs were significantly associated with etoposide IC₅₀ in combined, CEU and YRI population, respectively ($p < 0.0001$). Among them, 7, 56 and 6 SNPs were also significantly associated with gene expression of 6, 21 and 40 genes in combined, CEU and YRI population (Bonferroni corrected $p < 0.05$). The expression of 3, 18 and 24 genes whose expression were associated with SNP genotypes also significantly correlated with etoposide IC₅₀ in the three tested populations ($p < 0.05$). These include genes that may play a role in cancer (AGPAT2, IL1B and WNT5B) and genes not yet known to be associated with sensitivity to etoposide.

CONCLUSIONS: Using our genome-wide approach, we identified previously unknown genetic variants that contribute to cell sensitivity to etoposide-induced cytotoxicity. These genetic variants contribute to drug-induced toxicity through their effect on gene expression. This novel, unbiased method can be used to elucidate genetic variants contributing to a wide range of cellular phenotypes induced by chemotherapeutic agents.

OI-D-II

GENOME-WIDE ASSOCIATION STUDY TO IDENTIFY RISK FACTORS FOR DEVELOPING THERAPY-ASSOCIATED (SECONDARY)LEUKEMIA. A. A. Shinde, MD, PhD, G. Hayes, PhD, R. A. Larson, MD, R. A. Larson, MD, N. J. Cox, PhD, K. Onel, MD, PhD, University of Chicago, Chicago, IL.

BACKGROUND/AIMS: Therapy-related acute myelogenous leukemia (t-AML) is the most serious long-term complication of cancer chemotherapy. Only a subset of patients treated for cancer develop t-AML suggesting a genetic predisposition. We conducted a genome-wide association (GWA) study to investigate genetic factors associated with t-AML risk.

METHODS: A GWA scan using Affymetrix Mapping 10K arrays was performed on germline genomic DNA from 81 Caucasian individuals with t-AML and compared to previously genotyped 150 healthy Caucasian controls. Cases were adults with clinically diagnosed and cytogenetically characterized t-AML followed at the