OII-B-1

THE ROLE OF NA+-TAUROCHOLATE COTRANSPORTING POLYPEPTIDE (NTCP) IN THE HEPATIC UPTAKE OF ROSUVASTATIN. R. H. Ho, MD, Y. Wang, PhD, B. F. Leake, BS, H. Glaeser, PhD, W. Lee, PhD, C. J. Lemke, BS, R. G. Tirona, PhD, R. B. Kim, MD, Vanderbilt Univ. Medical Center, AstraZeneca, Nashville, TN.

BACKGROUND: Rosuvastatin is an HMG-CoA reductase inhibitor (statin) used in the treatment of dyslipidemia. Rosuvastatin is not subject to significant metabolism and we have previously shown a role of OATP transporters for rosuvastatin uptake.

AIM: We assessed the extent and relevance of bile acid uptake transporters to rosuvastatin uptake.

METHOD: The hepatic bile acid uptake transporter NTCP and the intestinal bile acid uptake transporter apical sodium-dependent bile acid transporter (ASBT) were expressed in HeLa cells utilizing a recombinant vaccinia system. Allelic variants of human NTCP were also assessed. NTCP expression relative to OATP mRNA was determined from a bank of human liver samples.

RESULT: We demonstrate the major human hepatic bile acid uptake transporter NTCP, but not rat Ntcp or ASBT, can transport rosuvastatin. Human hepatocyte studies suggest NTCP accounts for nearly 50% of rosuvastatin uptake. Remarkably, NTCP*2 (C800T; S267F), a variant associated with near complete loss of function for bile acid uptake, exhibited a profound gain of function for rosuvastatin uptake. Quantitative mRNA analysis revealed marked intersubject variability in expression of OATPs and NTCP.

CONCLUSION: NTCP may be a heretofore unrecognized transporter important to the hepatic uptake of rosuvastatin and possibly other drugs/statins in clinical use. Accordingly, expression and polymorphisms in NTCP may be an additional determinant of intersubject variability in response to statin therapy.

OII-B-2

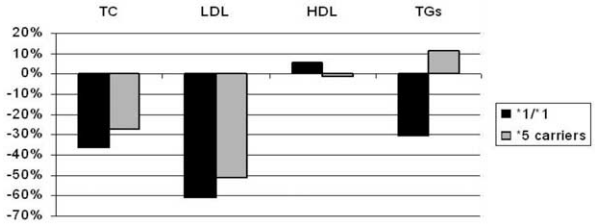
INFLUENCE OF SLCO1B1 (OATP1B1/OATP-C) GENE POLYMORPHISMS ON CHOLESTEROL RESPONSES TO ATORVASTATIN. I. Zineh, PharmD, T. Y. Langaee, PhD, MSPH, T. R. Wessel, MD, C. B. Arant, MD, R. S. Schofield, MD, University of Florida, Gainesville, FL.

BACKGROUND: The polymorphic *SLCO1B1* gene encodes for the OATP-C protein, which is important in hepatic uptake of many xenobiotics. The *5 allele has been recently shown to result in diminished hepatic uptake of atorvastatin, yet the clinical relevance is unclear. We hypothesized that *5 carriers would exhibit attenuated response to atorvastatin compared with wild-type homozygotes (*1/*1).

METHODS: 8-week treatment responses by genotype were assessed for 22 individuals without cardiovascular disease, N=18 for *1/*1 and N=4 for *5 carriers, treated with atorvastatin 80 mg daily. Genotype was assigned after allelic discrimination of Asn130Asp and Val174Ala polymorphisms by pyrosequencing (Asn130Val174=*1; Asn130Ala174=*5). Lipid profiles were determined by our university hospital clinical laboratory. Analyses were by general linear model with significance at $p<0.05$.

RESULTS: Baseline total cholesterol (TC), LDL, HDL, and triglycerides (TGs) were 186±39, 102±37, 61±15, and 117±76 mg/dl, with HDL higher in the *5 carriers (75 vs. 58 mg/dl, p=0.04). *5 carriers had 8.9%, 9.3%, 7%, and 42% less improvement in TC, LDL, HDL, and TGs, respectively, compared with *1/*1 (Figure). After controlling for baseline values, differences trended toward significance for TC (P=0.07) and LDL (P=0.09).

CONCLUSIONS: The *SLCO1B1* *5 allele may be associated with diminished lipoprotein responses to atorvastatin. The gene effect was most significant for TC and LDL and should be investigated in a larger population.



OII-B-3

EFFECT OF MATERNAL INFLAMMATION ON THE EXPRESSION OF ABCB1 AND ABCG2 IN PLACENTA. J. S. Wang, MSc, S. Teng, MSc, M. Piquette-Miller, PhD, University of Toronto, Toronto, ON, Canada.

BACKGROUND: The placenta serves as a protective barrier for the fetus. The drug efflux transporters P-glycoprotein (Pgp/ABCB1) and BCRP (ABCG2) are highly expressed in placenta and diminish fetal exposure to xenobiotics. As endotoxin has been shown to suppress the expression of Pgp in many tissues, we examined its effect on Pgp and BCRP expression in placenta, and its impact on the transplacental passage of the Pgp substrate, ^{99m}Tc-MIBI.

METHODS: Pregnant rats were administered endotoxin (LPS, 0.5, 1.0 mg/kg i.p.) or saline (control) on G17. Rats received ^{99m}Tc-MIBI (20 MBq i.v.) 20 h later, were sacrificed at 24 h, and tissues collected. ^{99m}Tc-MIBI levels were measured in fetal and placental tissues. Expression of Pgp and BCRP was examined by RT-PCR and Western blots.

RESULTS: As compared to controls, placental levels of *mdr1a*/Pgp mRNA were significantly reduced by 57 ± 3 % and 88 ± 4 % and BCRP mRNA levels were significantly reduced by 55 ± 8 % and 99 ± 0.1 % of control values in rats administered 0.5 or 1.0 mg/kg LPS, respectively. Dose-dependent reductions in the protein expression of Pgp and BCRP were observed. Likewise, 3.5-fold higher levels of ^{99m}Tc-MIBI were seen in the fetuses of LPS treated rats ($p < 0.05$).

CONCLUSIONS: Endotoxin-induced inflammation imposed significant down-regulation of placental Pgp and BCRP and increased fetal drug accumulation. Hence, maternal diseases can significantly alter the expression and activity of ABC transporters and thereby may contribute to altered fetal drug exposure.