PIII-51

IN UTERO EXPOSURE TO HMG-COA REDUCTASE INHIBITORS; EFFECTS ON FETAL AND NEONATAL OUTCOME. N. Taguchi, E. Rubin, A. Hosokawa, M. Moretti, S. Ito, The Hospital for Sick Children, Toronto, ON, Canada.

BACKGROUND: Since HMG-CoA reductase inhibitors (statins) are widely used for the treatment of hyperlipidemia in women of childbearing age, the pregnancy safety data regarding statins are urgently needed. Recent case series based on voluntary reports described cases of malformations including central nervous system defects and unilateral limb defects. This raised concerns about the fetal safety of statins. The objective of this study is to determine whether gestational use of statins poses substantial fetal toxicity.

METHODS:

–Design

A prospective, observational cohort study with a comparison group.

–Setting

A cohort based on a teratogen information service, The Motherisk Program.

–Participants

The women with exposure to a statin during the first trimester were matched with pregnant women, who have contacted us for information on use of known *non*-teratogen during pregnancy.

–Intervention

The data were collected by telephone interviews.

RESULTS: Pregnancy outcome of 45 exposed to statins and 45 matched comparison group were followed. There was no significant difference in the rate of major malformations between cases (1/45) and controls (3/45) ($p=0.38$). The pregnancy outcomes, such as live birth ($p=0.10$), spontaneous abortion ($p=0.72$), and therapeutic abortion were not statistically different between the exposed and control groups.

CONCLUSION: Our pilot cohort did not demonstrate the malformation patterns reported in a case series based on voluntary reports.

PIII-52

EFFECTS OF CIMETIDINE AND PROBENECID ON RENAL CLEARANCE OF NXY-059, A NOVEL NEUROPROTECTANT: A PHASE I STUDY TO DETERMINE THE TRANSPORTER RESPONSIBLE FOR ACTIVE SECRETION. Y. Cheng, S. Strid, O. Borgå, D. Nilsson, J. Wemer, AstraZeneca R&D, Borgå PK Consulting, Xendo Drug Development Services, Södertälje, Sweden.

BACKGROUND: NXY-059 is a novel free-radical trapping neuroprotectant that reduces infarct size and preserves brain function in animal models of acute ischemic stroke (AIS). In an initial Phase III study (SAINT I) NXY-059 has shown efficacy in AIS by reducing functional disability. NXY-059 is eliminated by renal excretion, primarily through glomerular filtration but with 30% estimated as active tubular secretion. This study was designed to further characterize the active renal excretion of NXY-059. Probenecid and cimetidine, substrates for renal systems that transport organic acids and bases, were chosen as model inhibitors.

METHODS: This was a single-center, randomized, open-label, parallel group study. 55 healthy subjects received a 12-h iv infusion of NXY-059 (target plasma concentrations 25-30 μmol/L) with one of these treatments given at 6 h:

Group A: Oral 1.5g probenecid
Group B: Oral 800mg cimetidine
Group C: Control

Renal clearance (CL_R) of NXY-059 was estimated before and after administration of the inhibitor.

RESULTS: The CL_R of NXY-059 in the probenecid group decreased by 30%, from an average of 108 mL/min (before 6 h) to 75.5 mL/min (after 6 h) [$p<0.001$]. There was no statistically significant difference in the mean CL_R of NXY-059 before and after 6 h for either the cimetidine or control group.

CONCLUSIONS: The active tubular secretion of NXY-059 occurs through an organic acid transporter, not an organic base transporter. This active secretion contributes approximately 30% of the renal elimination.

PIII-53

DISCORDANCE BETWEEN SLOW ACETYLATOR PHENOTYPE AND GENOTYPE FOR N-ACETYLTRANSFERASE 2 (NAT-2) IN A HMONG POPULATION. R. J. Straka, R. T. Burkhardt, N. P. Lang, T. Vang, K. Z. Hadsall, M. Y. Tsai, University of Minnesota, University of Arkansas, North Memorial Hospital, Minneapolis, MN.

BACKGROUND: Polymorphisms of NAT-2 acetylation contribute to drug toxicity, efficacy and cancer risk. Predominance of slow acetylation (SA) phenotype in ethnically distinct populations may have clinical implications for drug selection and cancer risk. The purpose of this study was to determine the genetic basis of SA phenotype predominance in Minnesota Hmong.

METHODS: Urine and DNA were obtained for phenotype and genotype analysis from unrelated healthy Hmong 18 and 65 years of age. Urinary molar ratios (MR) of caffeine metabolites (AFMU/1X) identified rapid acetylators (RA) phenotypes with a MR >= 0.6 and SA with MR < 0.6. Direct sequencing of the NAT-2 coding-region followed by cloning techniques for ambiguous genotypes identified individuals homozygous or heterozygous with a *4 and *13 allele as RA and variants as SA by genotype.

RESULTS: From 61 subjects (30±11 years, 27 male), analysis of 51 urine-DNA pairs identified 46 (90.2%) SA and 5 (9.8%) RA by phenotype. In contrast, genotypic analysis identified 5 (9.8%) SA and 46 (90.2%) RA. An 84% discordance between phenotype and genotype was observed. Direct sequencing did not reveal novel NAT-2 polymorphisms.

CONCLUSIONS: Genotypic analysis appears to demonstrate considerable discordance with the phenotype in Hmong. Genotyping alone, without a metabolic probe, would not have accurately predicted acetylation phenotype.

PIII-54

AN OPEN-LABEL, RANDOMIZED, 2-PERIOD, CROSSOVER STUDY, TO ASSESS THE EFFECTS OF MONTELUKAST ON THE PHARMACOKINETICS OF ROSIGLITAZONE, A CYP2C8 SUBSTRATE, IN HEALTHY ADULTS. E. Friedman, MS, R. Ramakrishnan, PhD, P. Larson, MS, K. Korzekwa, PhD, J. A. Wagner, MD, PhD, E. Migoya, PharmD, Merck & Co., Inc., Rahway, NJ.

BACKGROUND/AIMS: Recently published data indicate that montelukast (MONT) is a potent inhibitor of CYP2C8 *in vitro*. This study evaluated the effect of MONT on the clinical pharmacokinetics (PK) of rosiglitazone (ROSI), a known probe substrate for CYP2C8.

METHODS: In this open-label, randomized, 2-period, crossover study, 12 healthy adults received a single oral dose of ROSI 4-mg either alone and after oral administration of MONT 10-mg for 3 days. Blood samples were collected for determination of ROSI plasma concentrations in each treatment period.

RESULTS: The plasma PK of ROSI was not meaningfully altered upon co-administration of ROSI and MONT, as summarized in the table below. The median T_{max} of ROSI was 1 hr and the apparent $t_{1/2}$ of ROSI was ~4 hr after administration of both ROSI alone or upon co-administration with MONT. Both treatments were well tolerated; all adverse experiences were transient and rated as mild in intensity.

CONCLUSIONS: Administration of MONT 10-mg once daily for 3 days did not alter the plasma PK of a single dose of ROSI 4-mg demonstrating that MONT is not an *in vivo* inhibitor of CYP2C8-mediated metabolism.

Treatment	$AUC_{0-\infty}$ (ng · hr/ml)	C_{max} (ng/mL)	T_{max}* (hr)	Apparent.$t_{1/2}$** (hr)
ROSI + MONT	1656.09 (233.57)	284.00 (33.73)	1.0 (0.5-2.0)	4.3
ROSI	1620.03 (319.66)	280.74 (49.60)	1.0 (0.5-1.7)	4.5
GMR (ROSI + MONT/ROSI) and 90% CI	1.02 (0.95, 1.10)	1.01 (0.92, 1.11)	–	–

* Median (Range)
** Harmonic Mean