PI-117

EFFECT OF ROFECOXIB, ETORICOXIB, CELECOXIB, AND NAPROXEN ON URINARY EXCRETION OF PROSTANOIDS IN ELDERLY VOLUNTEERS. J. I. Schwartz, PharmD, MPH, K. Vandormael, MS, C. Thach, PhD, K. C. Lasseter, MD, G. B. Holmes, PharmD, J. L. Miller, BS, D. Hreniuk, BS, D. Hilliard, BS, K. M. Snyder, MS, B. J. Gertz, MD, PhD, K. M. Gottesdiener, MD, Merck & Co.,Inc., Clinical Pharmacology Associates, SFBCI, Rahway, NJ.

Purpose: COX-2 inhibitors (COX2i) and nonselective NSAIDs affect systemic and renal prostaglandin synthesis and may have differential effects on vasoactive eicosanoids [prostacyclin, PGI_2; thromboxane, TxB]. This study evaluated the effects of placebo (P), an NSAID [naproxen (N) 500 mg BID], and 3 COX2i [rofecoxib (R) 25 mg QD, etoricoxib (E) 90 mg QD, and celecoxib (C) 200 mg BID] on urinary prostanoids, 11-dehydro TxB_2 (TxB-M; systemic TxB production measure), and 2,3 dinor 6-keto $PGF_{1\alpha}$, (PGI-M; systemic PGI_2 production measure).

Methods: 152 patients (ages 60 to 85 yr) in 2 randomized, double-blind, placebo-controlled, 2-week parallel trials had prostanoids assayed from 8-hr urinary collections at pretreatment and Day 15.

Results: Effects were consistent for C, N, and P in both studies, so data for the 3 groups were pooled across trials. Results are below:

% Change from baseline in Urinary Excretion of Prostanoids (Mean SE)

Treatment	N	PGI-M	N	TxB-M
Rofecoxib	17	−58.9±4.6	17	−16.9±8.0
Etoricoxib	20	−58.3±4.4	21	0.9±8.9
Celecoxib	38	−58.2±2.9	38	−3.7±5.8
Naproxen	38	−75.1±1.7	38	−84.5±0.9
Placebo	37	−9.1±6.5	38	7.2±6.5

Conclusions: COX-2 inhibitors had similar but partial reductions ($p<0.89$) in PGI_2 synthesis [significantly less than that caused by naproxen ($p<0.05$)]. COX-2 inhibitors had no meaningful effect on systemic thromboxane [naproxen caused a substantial reduction ($p<0.05$) consistent with its effects on ex vivo serum TXB_2 production and platelet aggregation].

PI-118

INITIAL ANTIPYRINE DISPOSITION IN MAN IS ALTERED BY PROPRANOLOL. M. J. Avram, PhD, T. K. Henthorn, MD, C. U. Niemann, MD, C. A. Shanks, MD, T. C. Krejcie, MD, Northwestern University Feinberg School of Medicine, University of Colorado Health Sciences Center, University of California at San Francisco Medical School, Chicago, IL.

Purpose: β-Adrenergic antagonists decrease intravenous (IV) anesthetic dose requirements. The present study determined the effect of propranolol on antipyrine (AP) disposition from the moment of rapid IV injection using a recirculatory pharmacokinetic (PK) model. AP is a physiologic marker that distributes to a volume as large as total body water in a blood flow-dependent manner and is a surrogate for many lipophilic drugs, including IV anesthetics.

Methods: AP disposition was determined twice in 5 healthy adult males in this IRB-approved study, once during a propranolol infusion. After rapid AP injection, arterial blood samples were collected frequently for 2 min and less frequently thereafter. Plasma AP concentrations were measured by HPLC. AP disposition was characterized, using SAAM II, by a recirculatory PK model that describes drug disposition from the moment of injection. Parameters were compared using the paired t-test.

Results: The disposition of concomitantly administered indocyanine green (ICG) demonstrated that propranolol decreased cardiac output (C.O.) at the expense of the fast peripheral (nonsplanchnic) intravascular circuit. AP AUC was doubled for at least the first 3 min after rapid IV injection due to both decreased C.O. and maintenance of nondistributive blood flow at the expense of a two-thirds reduction of blood flow (intercompartmental clearance) to the rapidly equilibrating (fast, splanchnic) tissue volume.

Conclusion: The increase in AP AUC due to the propranolol-induced alteration of initial AP disposition could explain decreased IV anesthetic dose requirements in the presence of β-adrenergic blockade.

PI-119

EFFECT OF RIFAMPIN ON THE PHARMACOKINETICS OF ROSIGLITAZONE IN KOREAN HEALTHY SUBJECTS. J. Park, MD, K. Kim, PhD, W. Jung, MD, PhD, S. Kim, J. Shin, MD, PhD, Gachon Medical School, Seonam University College of Medicine, Inje University, Incheon, Republic of Korea.

Background and objective: Rifampin (INN, rifampicin) caused several drug interactions with several co-administered antidiabetic drugs. Rosiglitazone is a novel thiazolinedione anti-diabetic drug but little is known about the drug interaction between rifampin and rosiglitazone. Our objective was to investigate the effect of rifampin on the pharmacokinetics of rosiglitazone in humans.

Method: In a randomized two-way crossover study, 10 healthy Korean male subjects were treated once daily for six days with 600 mg rifampin or with placebo. On day 7, a single dose of 8 mg rosiglitazone was administered orally. Plasma rosiglitazone concentrations were measured.

Results: Rifampin significantly decreased the mean area under the plasma concentration–time curve for rosiglitazone by 65% (2947.9 versus 991.5 ng hr/ml; $P<0.001$) and the mean elimination half-life from 3.9 to 1.5 hours ($P<0.001$). The peak plasma concentration of rosiglitazone was significantly decreased by rifampin (537.7 versus 362.3 ng/ml; $P<0.02$). The apparent oral clearance of rosiglitazone increased about three-fold after rifampin treatment (2.8 versus 8.5 L/h; $P<0.001$).

Conclusion: This study showed that rifampin affects the disposition of rosiglitazone in humans, probably by the induction of CYP2C8 and to a lesser extent CYP2C9. Therefore, caution should be exercised during the co-administration of rifampin and rosiglitazone.

PI-120

PHARMACOKINETICS (PK) OF INTRAVENEOUS SCOPOLAMINE (SCP) PLUS PHYSOSTIGMINE (PHY) IN HEALTHY ELDERLY MALE AND FEMALE VOLUNTEERS. A. Men, MD, PhD cand., J. Venitz, MD, PhD, Virginia Commonwealth University, Richmond, VA.

Purpose: (1) To investigate the PK of SCP in healthy elderly volunteers, (2) To determine any PK interactions of PHY on SCP. **Methods:** Sixteen healthy elderly volunteers received 6.7μg/kg IV SCP/placebo, followed 60 minutes later by 6.7μg/kg IV PHY/placebo. Plasma SCP concentrations were measured by radio-receptor assay (LOQ: 100 pg/ml). Noncompartmental PK analysis was performed. ANOVA was used to assess gender, treatment and age differences. **Results:** CL_{tot} was 2.9±1.5 l/min (mean±SD), while Vd_{ss} was 249±106 l, resulting in a terminal half-life ($t_{1/2}$) of 72±19 min. No significant PK differences were found after co-administration of PHY. A gender difference was found for Vd_{ss} and $t_{1/2,}$ where males had a 45% higher Vd_{ss} and a 26% longer $t_{1/2}$ than females. Significant age differences were found for CL_{tot} and Vd_{ss}; the elderly showed higher values than those in the young. The following table shows PK parameters in the young (6M, 6F) and elderly healthy (8M, 8F) volunteers.

	Elderly Males	Elderly Females	Young Males	Young Females
CL_{tot} (l/min)	3.5 (1.9)	2.3 (0.5)	1.7 (0.2)	1.4 (0.5)
Vd_{ss} (l)	296 (128)	203 (55)	168 (52)	155 (60)

Conclusions: SCP showed rapid, extensive distribution and high clearance values suggesting extrahepatic metabolism. PHY did not have any influence on SCP PK. Gender differences were found in Vd_{ss} and $t_{1/2,}$ and age differences were found in CL_{tot} and Vd_{ss}, which may due to changes in plasma/tissue protein binding and/or extrahepatic metabolism.