PD-3

PK/PD MODELING OF THE INTERACTION BETWEEN IV SCOPOLAMINE (SCP) AND PHYSOSTIGMINE (PHY) IN HEALTHY ELDERLY VOLUNTEERS. Y. Men, MD, PhD, K. Wesnes, PhD, J. Venitz, MD, PhD, FDA, Cognitive Drug Research Ltd., VCU, Rockville, MD.

AIMS: 1. To assess the PK/PD interaction between IV SCP and PHY in elderly subjects; 2. To estimate *in vivo* muscarinic receptor affinities for SCP.

METHODS: In a randomized, placebo-controlled, four-way crossover clinical trial, sixteen volunteers (> 65 years) received 6.7μg/kg IV SCP/placebo, followed after 60 minutes by 6.7μg/kg IV PHY/placebo. An integrated SCP PK/PD model was used to simultaneously fit the plasma concentration and PD endpoints (heart rate, BPCHR, saliva flow, SF, simple reaction time, SRT, numerical working memory, NWM). A competitive PD model described the PD interaction between SCP and PHY.

RESULTS: SCP and PHY PK profiles fit two- and one compartment models, respectively. Median PK and PD parameter estimates (n= 16) are as follows:

PK Parameter	SCP	PHY	PD Parameter:	BPCHR [bpm]	SF [g/2 min]	SRT [ms]	NWM [ms]
V_1 [1]*	55	77	E_0	0	0	372	880
k_{12} [1/hr]	14.1		k_{co} [1/hr]		10	0.4	0.5
k_{21} [1/hr]	4.9		E_{max}	23 (Tachycardia)	−3.3	2314	6099
				−5 (Bradycardia)			
k_{10} [1/hr)	2.9	2.6	EC_{50} [ng/ml]	1.5(Tachycardia)	0.1	1.2	2.0
			n	4.1	1.3	2.3	1.5
			IC_{50} [ng/ml]	4.9	10	1.0	0.7

CONCLUSIONS: PHY IC_{50}s were estimated successfully: $IC_{50}^{CNS} < IC_{50}^{HR} < IC_{50}^{SF}$, which is helpful in predicting the clinical interaction between SCP and PHY in future studies. PK/PD modeling of SCP also succeeded in estimating EC_{50}s for CNS and PNS endpoints: $EC_{50}^{brady}(M_1) < EC_{50}^{SF}(M_3) < EC_{50}^{Tachy}(M_2)$. CNS effects may be attributed to central-M_2 receptors.

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PD-4

EFFECT OF NONMEM MINIMIZATION STATUS AND NUMBER OF REPLICATES ON BOOTSTRAP PARAMETER DISTRIBUTIONS FOR POPULATION PHARMACOKINETIC MODELS: A CASE STUDY. M. R. Gastonguay, PhD, A. El-Tahtawy, PhD, Metrum Research Group LLC, Purdue Pharma LLP, Avon, CT.

AIMS: Bootstrap (BS) parameter distributions are often used to characterize estimation uncertainty and determine confidence intervals (CI) for population pharmacokinetic (PPK) model parameters. These results are used to guide inferences about clinical relevance of covariate effects and other model components. The goal of this work was to compare BS parameter distributions using a published PPK model for oxaprozin (OX) under different minimization and resampling conditions.

METHODS: Nonparametric BS analyses with NONMEM were conducted on a PPK model for OX and resulting parameter distributions were summarized by: 1) number of BS replicates (REPS), and 2) minimization (MIN) and $COVARIANCE (COV) status.

RESULTS: For those runs reporting parameter estimates, BS CI for all parameters 1) did not change by more than 9% after 1000 BS REPS; 2) were unaffected by MIN status (<5% change), and most CI were unaffected by COV status (<5% change in all but 1 parameter).

CONCLUSIONS: The number BS REPS should be investigated for each problem, but a general estimate of 1000 REPS may be a useful starting point. MIN status did not affect BS CI for this case.

PD-5

DOES SEX INFLUENCE PROXIMAL SMALL INTESTINAL CYP3A OR P-GP EXPRESSION? M. F. Paine, RPh, PhD, S. S. Ludington, BS, M. L. Chen, PhD, P. W. Stewart, PhD, S. M. Huang, PhD, P. B. Watkins, MD, University of North Carolina, Food & Drug Administration, Chapel Hill, NC.

BACKGROUND: The higher systemic clearance of some CYP3A (whether also P-gp) drug substrates in women vs. men is attributed in part to a higher hepatic CYP3A4 content in women. This, combined with the lack of reported sex differences in the oral clearance of CYP3A substrates suggested a sex-dependent expression of CYP3A in the small intestine but in a pattern opposite to the liver.

METHODS: Duodenal biopsies obtained from healthy men (n=46) and women (n=45) were analyzed by Western blot for CYP3A4, CYP3A5, P-gp, and the control protein villin.

RESULTS: Among all subjects, CYP3A4 and P-gp content varied 8- and 10-fold, respectively. CYP3A5, which was readily detected in 27% of these predominantly Caucasian individuals, varied 7-fold. For all 3 proteins, a sex difference was not detected ($p \geq 0.55$). Comparing the 21 pre-menopausal women (all were aged <45 years) with the 43 men aged <45 years, again no sex differences were detected in CYP3A4 and P-gp content. While a difference in mean $\log_{10}$ (or median) P-gp content was not detected between the pre- and post-menopausal women, mean CYP3A4 content was 20% lower in the post-menopausal individuals ($p=0.01$).

CONCLUSIONS: The lack of a sex-dependent difference in proximal intestinal CYP3A4 and CYP3A5 could account in part for the lack of reported sex differences in the oral, relative to systemic, clearance of some CYP3A substrates. Ramifications of lower CYP3A4 content in post- vs. pre-menopausal women require further investigation.

PD-6

UREMIC TOXINS INHIBIT HEPATIC UPTAKE OF EPROSARTAN. H. Sun, MD, PhD, Y. Huang, MD, PhD, H. Okochi, PhD, L. Frassetto, MD, L. Z. Benet, PhD, University of California, San Francisco, San Francisco, CA.

BACKGROUND: Hepatic clearance of eprosartan (Epr) is significantly decreased in patients with end stage renal disease (ESRD). Uremic toxins may directly inhibit the transporter-mediated uptake and efflux thereby reducing hepatic clearance of Epr, which is not metabolized by CYPs.

METHODS: The inhibitory effects of the uremic toxins, CMPF and indoxyl sulfate, on uptake transporters (rOatp2 and hOATP-C) and the efflux transporter (P-gp) were examined using transient transfected HEK293 cells and MDR1-MDCK cells, respectively. The effects of these uremic toxins on Epr uptake were further evaluated in rat hepatocytes and hOATP-C transfected cells.

RESULTS: Both CMPF and indoxyl sulfate exhibited dose-dependent inhibition of rOatp2 and hOATP-C. The IC_{50}s of CMPF on rOatp2 and hOATP-C mediated uptake of estrone sulfate (1 μM) were 25 μM and 55 μM, respectively. Indoxyl sulfate is a weaker inhibitor of rOatp2 and hOATP-C with IC_{50}s of 97 μM and 397 μM, respectively. Both uremic toxins had no effects on P-gp. The uptake of Epr was mainly mediated by rOatp2 in rat. At 200μM, CMPF significantly inhibited Epr uptake by 53% in rat hepatocytes. The uptake of Epr was mediated by OATP-C in human hepatocytes with a K_m value of 12.5 ± 0.3 μM. CMPF dose-dependently inhibited Epr (5 μM) uptake by hOATP-C with an IC_{50} of 125.9 ± 1.3 μM.

CONCLUSION: Our study suggests that the inhibitory effect of CMPF may at least partially contribute to the reduced hepatic clearance of Epr in ESRD patients.