PI-115

EFFECTS OF VARYING DEGREES OF RENAL IMPAIRMENT ON THE PHARMACOKINETIC DISPOSITION OF NEBIVOLOL. A. A. Shaw, PhD, S. Liu, MS, L. F. Zachwieja, BS, T. Eddy, BS, C. M. Donnelly, MS, M. Y. Huang, PhD, Mylan Pharmaceuticals Inc, Morgantown, WV.

BACKGROUND: Nebivolol (N) is believed to be a unique cardiovascular agent studied worldwide for the treatment of HTN, CHF and other cardiovascular conditions owing to its vascular endothelial nitric oxide modulating capabilities and its highly selective β_1-antagonism. It is extensively metabolized with <0.1% of unchanged nebivolol excreted in urine. The present study examined what effect, if any, renal impairment has on oral N or its separate enantiomers.

METHODS: Twenty-one subjects were divided into 3 renal impairment categories (mild, moderate, severe) based upon either measured (24-hour urine collection) or calculated (by Cockroft-Gault equation) creatinine clearance. Four healthy subjects, matched for age, gender, weight, and smoking habit, were selected as a control group.

RESULTS: N (5 mg) was well tolerated with C_{max} and T_{max} being comparable across renal function classifications. Similar results were seen for the enantiomers and the active nebivolol glucuronide metabolites.

Category	AUC_∞ (ng hr/mL)	90% CI	Cl/F (L/hr)	90% CI
Healthy (n = 4)	6.59	N/A	891	N/A
Mild (n = 7)	4.55	0.34–1.47	1241	0.73–2.05
Mod. (n = 9)	11.28	0.70–3.07	738	0.17–1.49
Severe (n = 5)	23.36	1.22–5.92	416	0–1.17

CONCLUSIONS: Since apparent clearance is significantly diminished in patients with severe renal impairment, dose adjustment may need to be considered, an unexpected finding given N's lack of renal excretion.

PI-116

EFFECT OF CHRONIC ADMINISTRATION OF FLUOXETINE ON THE PHARMACOKINETICS OF NEBIVOLOL. A. A. Shaw, PhD, S. Liu, MS, L. F. Zachwieja, BS, C. M. Donnelly, MS, M. Y. Huang, PhD, Mylan Pharmaceuticals Inc, Morgantown, WV.

BACKGROUND: Nebivolol (N) is considered a unique racemic cardio-selective β_1-antagonist with vascular endothelial nitric oxide modulating capabilities that undergoes extensive metabolism to active moieties via the CYP2D6 enzymatic pathway. Fluoxetine (F), one of the most studied potent inhibitors and substrates of CYP2D6 enzyme used clinically, was selected to assess the potential interactions with N.

METHODS: Ten CYP2D6 extensive metabolizers (EM) received an oral 10 mg dose of N on Day 1, an oral 20 mg dose of F QD on Days 8 through 27, and 10 mg N plus 20 mg F on Day 28. PK estimates for N were assessed.

RESULTS:

Parameter	Day 1	Day 28	Ratio	90% CI
AUC_∞ (ng hr/mL)	13.87	92.33	6.02	4.57–7.91
C_{max} (ng/mL)	2.33	5.45	2.27	1.83–2.80
T_{max} (hr)	1.30	2.60	2.00	1.58–2.42
$t_{1/2}$ (hr)	12.51	17.45	1.40	1.07–1.72
Cl/F (L/hr)	787.0	142.9	0.18	0.014–0.35

Co-administration of N with F was well tolerated.

CONCLUSIONS: The results confirm N's reliance on the CYP2D6 enzymatic pathway for elimination. The elevated N plasma concentrations seen with the co-administration of F were considerably lower than the clinically safe and well-tolerated levels of N alone previously observed in poor metabolizer subjects (AUC_∞: 614 ng·hr/mL; C_{max}: 9.21 ng/mL).

PI-117

LACK OF INTERACTION BETWEEN R483, A NOVEL PEROXISOME PROLIFERATOR-ACTIVATED RECEPTOR GAMMA AGONIST, AND DRUGS METABOLIZED BY CYP2C9 AND CYP2C19. C. Weber, PhD, B. Kuhn, BSc, B. Fotteler, MSc, C. Funk, PhD, F. Hoffmann-La Roche Ltd, Basel, Switzerland.

BACKGROUND/AIMS: Treatment with PPARγ agonists improves insulin sensitivity in patients with type 2 diabetes. R483 is a potent PPARγ agonist in clinical development. Based on R483's in vitro inhibition potential for CYP2C9 and CYP2C19 substrates an in vivo interaction at therapeutic doses could not be excluded completely. The potential interaction of R483 with warfarin and mephenytoin, substrates of CYP2C9 and CYP2C19, respectively, was investigated in vivo.

METHODS: Two open label, randomized, crossover trials in healthy male volunteers investigated the effect of a 40 mg single dose of R483 on the PK and PD of a 26 mg single dose of warfarin and on the PK of a 100 mg single dose of mephenytoin. Prothrombin time and factor VII activity were assessed as PD markers of warfarin action. C_{max} and $AUC_{0-\infty}$ of S-warfarin were used as primary PK parameters. The urinary S/R isomeric ratio of mephenytoin was assessed as the primary PK parameter of mephenytoin.

RESULTS: R483 did not interfere with the PK or PD of warfarin, nor did it affect the metabolism of S-mephenytoin.

CONCLUSIONS: R483 does not interact with drugs metabolized by CYP2C19 and CYP2C9. Taking into account in vitro data any drug-interaction via inhibition of all major CYP450 isoenzymes is unlikely for R483.

PI-118

BIOAVAILABILITY AND INTRACELLULAR PHARMACOKINETICS OF AZITHROMYCIN IN PATIENTS WITH CYSTIC FIBROSIS. L. Bi, MS, K. M. Huynh, S. Louie, PharmD, N. Hoem, PhD, J. Kriengkauykiat, PharmD, M. Gill, PharmD, P. Beringer, PharmD, University of Southern California, MDS Pharma, Los Angeles, CA.

BACKGROUND: Azithromycin (AZM) significantly improves pulmonary function in patients with cystic fibrosis (CF). Our hypothesis is that the absorption of AZM may be altered in CF due to pancreatic insufficiency. Additionally, MDR1 and CFTR are coordinatley regulated which may alter the intracellular disposition of P-gp substrates. The objective is to compare the bioavailability and intracellular (IC) concentrations of AZM in patients with CF and healthy volunteers (HV).

METHODS: A prospective, randomized, controlled crossover study involving 12 CF patients and 11 age-matched HV. In period I, all subjects received either a single PO or IV dose of AZM followed by crossover with one week washout. In period II, all patients received AZM QOD×3d. Blood and PBMC samples were obtained at specified times, and were assayed using LC-MS/MS. PK analysis was performed using a 3-compartment model with ADAPT II. Differences between groups were determined using Mann-Whitney test.

RESULTS: The rate and extent of absorption did not differ between the two groups. Distribution to the peripheral compartment was greater in the HV which may be attributed to greater adipose when compared with the CF patients. AZM demonstrates significant penetration into PBMCs in both groups. No significant differences in IC PK between groups were noted.

CONCLUSION: No alteration in dosage of AZM is necessary in patients with CF taking pancreatic enzymes. The prolonged intracellular half-life supports the current QOD dosing strategy.

	PK results Median (SD)		
	CF	HV	P
Ka (h-1)	0.48 (0.88)	0.45 (0.27)	0.60
F (%)	34.8 (13.5)	40.1 (17.8)	0.34
$C_{serum\ 52h}$ (ng/ml)	19.3 (10.3)	21.9 (9.7)	0.61
$C_{PBMC\ 72h}$ (mcg/ml)	9.7 (8.9)	13.3 (7.3)	0.55
T 1/2 PBMC (h)	77.0 (37.0)	92.0 (23.1)	0.85