

PII-119

A CYP3A4 INHIBITOR INCREASED THE EFFECT OF CABERGOLINE IN THE TREATMENT OF PARKINSON'S DISEASE. A. Nakatsuka, M. Nagai, H. Yabe, T. Moritoyo, M. Nomoto, Clinical Pharmacology and Therapeutics, Ehime University School of Medicine, Clinical Pharmacology and Therapeutics, Ehime University School of Medicine, Touonshi Shigenobu-cho Shitsukawa, Japan.

INTRODUCTION: Cabergoline is a synthetic ergote dopamine agonist that is metabolized by CYP3A4, is applied in the treatment of Parkinson's disease (PD). Clarithromycin, one of macrolide antibiotics, is a potent inhibitor of the CYP3A4. We studied the effect of coadministration of clarithromycin with cabergoline in healthy male volunteers and in patients with PD.

METHODS: Trial1: Ten healthy male volunteers were enrolled. Subjects were randomized to take a single oral dose of cabergoline 1mg/day for 6 days, or a single oral dose of cabergoline plus clarithromycin 400mg/day for 6 days.

Trial2: Seven patients with PD who treated with cabergoline were enrolled. They were evaluated with their symptoms of PD and blood concentration of cabergoline before and after the coadministration with clarithromycin for 6 days.

RESULTS: In healthy male volunteers, the mean of C_{max} and AUC of cabergoline increased around 2.7 times by coadministration of clarithromycin. In patients with PD, the blood concentration of cabergoline increased 1.73 times and three of 7 patients showed improvement in their PD sign through coadministration.

CONCLUSION: Coadministration with clarithromycin may increase the effect of cabergoline on the treatment of PD.

PII-120

ABSORPTION, METABOLISM, AND EXCRETION OF (³H)-OSPEMIFENE FOLLOWING A SINGLE ORAL DOSE TO POST-MENOPAUSAL WOMEN. S. Bryson, PhD, K. Cornelissen, PhD, M. Anttila, MSc, Covance CRU, Hormos Medical Corporation, Leeds, United Kingdom.

BACKGROUND/AIMS: Ospemifene is a novel selective oestrogen receptor modulator being developed for osteoporosis. The aims were: to evaluate the pharmacokinetics of total radioactivity, unchanged ospemifene, and the major metabolite 4-hydroxyospemifene; to obtain mass balance by quantifying the urinary and faecal excretion of radioactivity; to examine the pattern of metabolites in plasma, urine and faeces and the *ex-vivo* plasma protein binding of total radioactivity and ospemifene.

METHODS: A single oral dose (60 mg) of ospemifene, containing 20.2 MBq (³H)-ospemifene, was administered orally to 6 healthy post-menopausal women. Blood, urine and faeces sampling was performed up to 240 h post-dose.

RESULTS/CONCLUSIONS: Ospemifene was rapidly absorbed (t_{max} 0.75–3 h) and steadily eliminated (t_{1/2} of 25–29 h). 4-hydroxyospemifene underwent formation rate-limited elimination with t_{max} similar to the parent drug. Radioactivity was mainly faecally eliminated, with 75% of the dose being recovered over 240 h, with 7% eliminated in urine. Ospemifene and total drug-related material were extensively plasma protein bound (93–98%) with minimal binding to blood cells. Ospemifene metabolism was extensive with several radiolabelled metabolites in plasma, urine and faeces.

PII-121

NO EFFECT OF CONCOMITANT ADMINISTRATION OF NEBIVOLOL AND LOSARTAN IN HEALTHY VOLUNTEERS GENOTYPED FOR CYP2D6 STATUS. T. E. Lawrence, PhD, C. Chien, PhD, H. C. Tu, MS, J. M. Phillips, RN, C. M. Donnelly, MS, M. Y. Huang, PhD, Mylan Pharmaceuticals Inc., Morgantown, WV.

BACKGROUND: Nebivolol (N) has been shown through a number of studies to be a cardioselective β₁-antagonist with vascular endothelial nitric oxide releasing capabilities that exhibits CYP2D6-mediated polymorphic metabolism. Losartan (L), an ARB, is extensively metabolized by CYP2C9 (a known polymorphic enzyme) and is likely to be used concomitantly. This study examined if coadministration of N and L alters the pharmacokinetic (PK) characteristics of either agent, or the active metabolite of L, EXP-3174.

METHODS: This open-label study was conducted in 24 subjects, genotyped for CYP2D6 status (EM n=20; PM n=4). Using a two-sequence, two-treatment design, single doses of 10 mg N (Day 1 or 29), 50 mg L (Day 1 or 29), or their combination (Day 15) were given. Blood samples for PK assessment were taken on Days 1, 15 and 29.

RESULTS:

Parameter	C _{max}		AUC _{0-∞}	
	Ratio	90% CI	Ratio	90% CI
EM-N	0.80	0.68–0.93	0.89	0.82–0.97
PM-N	0.93	0.76–1.14	0.94	0.68–1.29
L	0.89	0.77–1.02	0.86	0.81–0.92
EXP-3174	0.94	0.86–1.03	0.98	0.94–1.02

CONCLUSION: There were no clinically meaningful changes observed in the PK of either L or N, confirming that the two agents should be capable of being safely co-administered.

PII-122

AN OPEN-LABEL, RANDOMIZED, SINGLE-DOSE, DOSE-PROPORTIONALITY STUDY OF ORAL DOSES OF A SUSTAINED-RELEASE FORMULATION OF DESVENLAFAXINE SUCCINATE IN HEALTHY SUBJECTS. J. A. Behrle, MS, A. I. Nichols, PhD, S. B. McGrory, RN, BSN, D. Raible, MD, Wyeth Research, Collegeville, PA.

BACKGROUND/AIMS: To assess the dose-proportionality of single oral doses of a sustained-release formulation of desvenlafaxine succinate (DVS-SR) in healthy subjects.

METHODS: A randomized single-dose crossover study was conducted in 24 healthy male subjects. Three (3) doses (100, 300, and 600 mg) were given by using 100-mg tablets after a medium-fat breakfast. Routine laboratory tests, vital signs, and electrocardiograms (ECG) were measured throughout the study. Plasma concentrations of desvenlafaxine (DV) were analyzed by model-independent methods and linear dose proportionality of C_{max} and AUC were assessed by an exponential regression model.

RESULTS: DV was slowly absorbed (mean t_{max} of 7 to 8 hours) with slow elimination (mean t_{1/2} of 11 hours). C_{max} and AUC increased linearly over the dose range of 100 to 600 mg. The between-subject variability was low with the percent coefficient of variations (%CV) under 25% for C_{max}, t_{1/2}, and AUC. Nausea and dizziness were the most common adverse events. No clinically relevant changes occurred in ECG intervals and laboratory tests.

CONCLUSION: Increases in the C_{max} and AUC of DV were linear over the dose range studied (100, 300, and 600 mg). DVS-SR was generally well tolerated at all doses.