

## PII-102

PHARMACOKINETIC STUDY ON THE INTERACTION BETWEEN CABERGOLINE AND CLARITHROMYCIN IN HEALTHY VOLUNTEERS AND PATIENTS WITH PARKINSON'S DISEASE. M. Nomoto, MD, PhD, T. Nomura, MD, PhD, A. Nakatsuka, M. Nagai, MD, PhD, Y. Yabe, MD, Ehime University School of Medicine, Shigenobu, Japan.

Pharmacokinetic interaction between cabergoline, a dopamine receptor agonist and a macrolide, clarithromycin was studied in healthy volunteers and patients with Parkinson's disease. Ten healthy volunteers with the age between 23 to 50 years were employed in an open, two periods, crossover study for the pharmacokinetics of cabergoline. Cabergoline was administered at the dose of 1 mg per day for 6 days with or without clarithromycin at the dose of 400 mg per days. The blood was sampled on the day 1 and on the day 6. Domperidone, a antiemetic agent was given at the dose of 10 mg with cabergoline. Coadministration of clarithromycin increased the C<sub>max</sub> from 55.4 to 152.9 pg/ml, and the AUC from 482 to 1268 pg/ml hr. Coadministration of clarithromycin increased bioavailability of cabergoline 2.8 times as high as clarithromycin alone. Administration of clarithromycin on patients with Parkinson's disease also increased the bioavailability of cabergoline 2-4 times as high as cabergoline alone. The metabolism of cabergoline through CYP3A4 would be suppressed by clarithromycin. Clarithromycin was an antibiotics applied to upper airway or skin infectious disorders. Coadministration of clarithromycin or other CYP3A4 inhibiting agents may increased the bioavailability of ergot alkaloid dopamine receptor agonists, and increased the antiparkinsonian effect of agents in patients with Parkinson's disease.

## PII-103

EVALUATION OF HERBAL PRODUCTS AS POTENTIAL INHIBITORS OF MDR1. G. K. Dresser, MD, W. McDonald, BSc, R. B. Kim, MD, D. G. Bailey, PhD, Lawson Health Research Institute, Vanderbilt University Medical Center, London, Canada.

Herb-drug interactions are increasingly noted to be a potentially preventable cause of drug toxicity or loss of therapeutic efficacy. In addition to their effects on CYP enzymes, phytochemicals in St. John's wort and grapefruit juice are reported to interact with the drug efflux transporter, P-glycoprotein (P-gp)/MDR1. However, the potential effects of other popular, phytochemical rich herbs on MDR1 function have not been established.

Ethanollic extracts of several herbal products were prepared. Bidirectional digoxin transport was determined across polarized Caco-2 cells containing P-gp. Herbal extracts were added to apical and basal compartments. Inhibitory effects of the herbal extracts were compared to verapamil 20 uM (positive control) and ethanol 2.5% (negative control). Viability of Caco-2 monolayer was confirmed by measuring inulin leak.

Black Cohosh and St. John's wort were the most potent inhibitors of P-gp and completely abolished digoxin transport. The effect at 1.25 mg/ml was comparable to that of verapamil 20 uM. Echinacea, Feverfew, and Valerian inhibited digoxin transport by 70-80%. Ginseng and Perilla at similar concentrations did not affect digoxin transport. Kava and Garlic extracts appeared to compromise the integrity of the Caco-2 monolayer.

Additional studies of Black Cohosh, Echinacea, Feverfew and Valerian are needed to determine the potential clinical relevance of these findings.

## PII-104

METABOLITE PATTERNS MEASURED DURING REPEATED DOSING OF ACETAMINOPHEN (APAP) AT 4, 6, AND 8 G/DAY IN HEALTHY ADULTS. C. K. Gelotte, PhD, J. F. Auiler, MS, J. M. Lynch, MD, A. R. Temple, MD, J. T. Slattery, PhD, D. L. Bowen, MD, McNeil Consumer & Specialty Pharmaceuticals, University of Washington, Fort Washington, PA.

We assessed the pharmacokinetics (PK) and metabolism of 1, 1.5, and 2 g APAP dosed every 6 h for 3 days (4, 6, and 8 g/d) using a double-blinded, placebo-controlled, 3-regimen study design. Subjects were divided into 2 groups that received: (I) placebo (n=6) or APAP (n=12) at 4 then 6 g/d; (II) placebo (n=6) or APAP (n=12) at 4 then 8 g/d. Safety and hepatic function were monitored daily. Blood samples were collected after the first and last dose of each dosing regimen, and urine was collected for 24 hours on Day 3 of dosing. PK results showed that APAP plasma concentrations did not accumulate with repeat doses, and that steady-state concentrations were linearly related to dose. Plasma metabolite data showed an unexpected increase in production of the major metabolite APAP-glucuronide and a decrease of APAP-sulfate between the first and last doses for 4, 6, and 8 g/d. The urine metabolite pattern changed with dose level: a higher amount (67%) of APAP-glucuronide was produced at 8 g/d compared with 59% and 61% for 4 and 6 g/d, and a lower amount (11%) of APAP-sulfate was produced at 8 g/d compared with 19% and 14% for 4 and 6 g/d. The findings are consistent with enzyme induction of glucuronidation and saturation of the sulfate pathway. Patterns of the other metabolites (thiols and catechol) did not differ substantially with dose. All doses were well tolerated and all hepatic aminotransaminase values stayed within normal limits.

## PII-105

EFFECT OF R411, A DUAL  $\alpha4/\beta1$ - $\alpha4/\beta7$  INTEGRIN ANTAGONIST BEING DEVELOPED FOR ASTHMA, ON THE ACTIVITIES OF THE MAJOR DRUG METABOLIZING ENZYMES AFTER ORAL ADMINISTRATION IN HEALTHY SUBJECTS. R. Abbas, PhD, Y. Hijazi, J. Tang, L. Renzetti, A. Rames, H. Welker, Hoffmann-La Roche, Inc, Nutley, NJ.

R411 is a novel agent under development for chronic treatment of asthma. It is rapidly and completely converted to its active metabolite, RO027-0608. The objective of this study was to assess the effect of oral administration of R411 on the activity of the major drug-metabolizing enzymes: CYP3A, CYP1A2, CYP2D6, CYP2C19, and CYP2E1, using a multi-probe drug cocktail. Twelve healthy male subjects were enrolled in this single-center, one-sequence crossover, open-label study. Each subject received a single daily oral tablet dose of 300 mg R411 for 8 days. Three days before and 8 days after R411 administration subjects received a 5-drug combination consisting of single oral doses of 100 mg caffeine, 250 mg chlorzoxazone, 100 mg mephenytoin, 100 mg dapsone, and 10 mg debrisoquine in order to determine activity of the principal CYP450 enzymes. Serial blood and urine samples were collected to determine the drug's concentration. The ratio of the least square means together with their 90% CI for all enzyme activities lies within 80-115 boundaries except for CYP2C19 where the ratio (90% CI) lies between 75-120 boundaries. These results indicate no clinically relevant interaction between R411 and any of the substrates of the CYP3A, CYP1A2, CYP2D6, CYP2C19, and CYP2E1. In conclusion, the drug was well tolerated with no safety concerns after multiple doses. R411 had no effects on the enzyme activities tested, suggesting a low potential for CYP450 drug-mediated interactions.