PDII-A-3

EFFECTS OF RIFAMPIN ON THE PHARMACOKINETICS AND PHARMACODYNAMICS OF GLICLAZIDE. J. Park, MD, K. Kim, PhD, J. Shin, MD, PhD, Gachon Medical School, Kyung-Hee University, Inje University, Incheon, Korea.

Objective: Rifampin is a potent inducer of several cytochrome P450 (CYP) enzymes. Gliclazide is a sulfonylurea antidiabetic drug, suggested to be metabolized by CYP2C9. Our aim of this study was to evaluate the effect of rifampin on the pharmacokinetics and pharmacodynamics of gliclazide.

Method: In a randomized, two-phase crossover study, 9 healthy subjects were treated for 6 days with 600 mg rifampin or placebo once daily. On day 6, a single oral dose of 80 mg gliclazide was administered. Plasma gliclazide and blood glucose concentrations were measured.

Results: Rifampin decreased the mean area under the plasma concentration-time curve of gliclazide by 69.8 % ($p<.001$) and the mean elimination half-life from 9.5 to 3.3 hours ($p<.05$). The clearance of gliclazide increased about 4-fold after rifampin treatment ($p<.001$). Significant difference in the blood glucose response to gliclazide was observed between placebo and rifampin phase.

Conclusion: The effects of rifampin on the pharmacokinetics of gliclazide suggest that rifampin induced the CYP2C9-catalyzed metabolism of gliclazide. Concomitant use of rifampin with gliclazide can lead to a considerably reduced glucose-lowering effect of gliclazide.

PDII-A-4

EVALUATION OF THE PHARMACODYNAMIC AND PHARMACOKINETIC INTERACTION BETWEEN PAGOCLONE AND ETHANOL. G. M. Haig, PharmD, B. Giordani, PhD, E. J. Randinitis, PhD, D. Y. Mitchell, PhD, Pfizer Global Research and Development, The University of Michigan, Ann Arbor, MI.

Purpose Pagoclone, a partial $GABA_A$ receptor agonist, is being developed for treatment of anxiety disorders. This study determined the pharmacokinetic (PK) and pharmacodynamic (PD) interaction between ethanol (EtOH) and pagoclone. **Methods** Study design was a double-blind, 4-way crossover in 16 healthy women aged 25-54. Pagoclone 0.6mg BID or placebo was administered for 5 days. After the last pagoclone dose, EtOH 0.7gm/kg or placebo-equivalent EtOH (0.4%) was administered. Blood collections for EtOH, pagoclone, and PD0302772 (active metabolite) assays, and neuropsychometric testing were conducted serially. **Results** The incidence of CNS and GI adverse events was high, and similar, among subjects receiving EtOH and EtOH/pagoclone. Cmax for EtOH alone was 1.2 mg/mL, and EtOH with pagoclone was 1.0 mg/mL, indicating intoxicating EtOH plasma concentrations. EtOH, pagoclone and PD0302772 Cmax and AUC met the standard bioequivalence criteria. Generally, the treatment rank order of neuropsychometric performance (worst to best) was: pagoclone/EtOH>EtOH≫pagoclone>placebo. Pagoclone did not express synergistic effects with EtOH. Pagoclone had additive effects to EtOH in motor screening and in part of a memory test. **Conclusion** No PK or synergistic PD interaction was observed between pagoclone and EtOH. Pagoclone exhibited few additive effects. However, since individual responses to CNS medications and EtOH may vary, patients should be cautioned about combining EtOH and pagoclone.

PDII-A-5

EFFECTS OF AMITRIPTYLINE, GABAPENTIN, AND CARBAMAZEPINE ON MORPHINE-INDUCED RESPIRATORY DEPRESSION IN RABBITS. Eran Kozer, MD, Zina Levichek, MD, Noriko Hoshino, MD, Bushan Kapur, PhD, John Leombruno, Gideon Koren, MD, Shinya Ito, MD. Division of Clinical Pharmacology and Toxicology, The Hospital for Sick Children, Toronto, Ontario, Canada.

Although opioids remain the most effective treatment for severe pain, tricyclics and anticonvulsants have been proven useful for chronic neuropathic pain. However, data on the drug interactions of these drugs and opioids are limited. This study was undertaken to characterize effects of chronic use of gabapentin, amitriptylin, and carbamazepine on respiratory depression induced by morphine.

Methods: Five groups of rabbits received for 5 days saline (Group 1), amitriptyline 7mg/kg bid (Group 2), carbamazepine 100 mg/kg bid (Group 3), or gabapentin 25mg/kg bid (Group 4). Group 5 received the three drugs concurrently. On day 5 morphine 5mg/kg was given intravenously. Respiratory parameters including arterial PCO_2 and morphine serum concentrations were measured repeatedly.

Results: PaCO2 was higher ($p<0.05$) throughout the study period in Groups 2 and 5. Peak PaCO2 in Group 2 (59 ± 2mmHg), and Group 5 (57 ± 1mmHg) were significantly ($p<0.001$ and $p=0.007$) higher than in Group 1(49 ± 6mmHg). The area under the PaCO2 versus time curve was significantly higher in Groups 2, 5 ($p<0.001$) and 4 ($p<0.05$) than in Group1. There were no significant differences between the groups in morphine serum concentrations.

Conclusions: Amitriptyline, and gabapentin potentate morphine-induced respiratory depression without changing the serum concentrations. Morphine doses need to be reduced if the patient is also receiving amitriptylin and/or gabapentine.

Supported by the Hospital for Sick Children

PDII-A-6

CYP3A AND P-GLYCOPROTEIN INDUCTION WITH ST. JOHN'S WORT IN HEALTHY VOLUNTEERS OF SELECTED ETHNIC POPULATIONS. R. Xie, PhD, L. Tan, MD, E. C. Polasek, MD, C. Hong, M. Teillol-Foo, MD, T. Gordi, PhD, A. Sharma, PhD, E. J. Antal, PhD, Pharmacia, Singapore.

The inducibilities of CYP3A and P-glycoprotein (Pgp) by St. John's Wort (SJW) in six ethnic groups (White, Black, Hispanic, Chinese, Indian, and Malay) were investigated. Thirty healthy subjects (5/group) received single dose of fexofenadine (60mg), midazolam oral (5mg) and IV (2mg, at 6hr after oral dose) on Day1 and Day11. SJW (300mg) was given three times a day on Day2 through Day11. Pharmacokinetic (PK) parameters on Day1 (baseline) and Day11 (with SJW) of midazolam and fexofenadine were determined by non-compartment analysis. Oral clearances (CLpo) of fexofenadine from all subjects were 77 ± 34 L/h on Day1 and 132 ± 64 L/h on Day11. Day 11 CLpo was significantly different from Day1 ($p<0.001$), but no significant differences were detected between ethnic groups. The terminal half-lives on Day1 and Day11 were similar.

The absolute bioavailability (F), hepatic (FH), and intestinal (FG) availabilities of midazolam on Day1 were 0.20 ± 0.04, 0.73 ± 0.08 and 0.28 ± 0.06, respectively. On Day11, F, FH and FG were 0.11 ± 0.04, 0.59 ± 0.09 and 0.19 ± 0.06, respectively. The systemic clearance (CL) of midazolam were 16 ± 5 L/h (Day1) and 25 ± 5 L/h (Day11). The F and CL on Day11 were significantly different from Day1 ($p<0.001$), but the parameter ratios (Day11/Day1) were similar between ethnic groups. In conclusion, SJW induces CYP 3A4 and intestinal Pgp and intestinal CYP 3A4 was induced to greater extent than that in liver. Inducibilities between ethnic groups appeared similar.