5.72, 10.0, and 4.45 mL/min/kg for treatments I-IV, respectively) and renal clearance (1.44, 1.87, 6.78, and 1.72 mL/min/kg) of torasemide and total amount of unchanged torasemide excreted in 8-h urine (Ae 0-8 h, 694, 780, 1310, and 1040 μg) in treatment III were considerably faster (or greater) than those in treatments I, II, and IV. Although the difference in Ae 0-8 h between treatments I and III were only 88.8%, the diuretic and/or natriuretic effects of torasemide were markedly different among the four treatments. For example, the mean 8-h urine output was 101, 185, 808, and 589 mL for treatments I-IV, respectively, and the corresponding values for sodium excretion were 10.1, 20.6, 89.2, and 29.9 mmol and for chloride excretion were 14.5, 27.9, 94.0, and 37.2 mmol. The present findings are as follows. 1) Although full fluid replacement was employed in both treatments III and IV, the 8-h diuretic, natriuretic, and chloruretic effects in treatment III were significantly greater than those in treatment IV indicating the importance of the composition of fluid replacement. 2) Both treatments I and IV received no sodium replacement, however, the 8-h diuretic, natriuretic, and chloruretic effects were significantly greater in treatment IV than those in treatment I indicating the importance of rate of fluid replacement for the diuretic effects. Some implications for the bioequivalence evaluation of dosage forms of torasemide are discussed.

[PE2-15] [04/18/2003 (Fri) 09:30 - 12:30 / Hall P]

Dose-Independent Pharmacokinetics of a New Reversible Proton Pump Inhibitor, KR-60436, after Intravenous and Oral Administration to Rats: Gastrointestinal First-Pass Effect

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Dose-independent pharmacokinetic parameters of KR-60436, a new proton pump inhibitor, were evaluated after an intravenous, iv (5, 10, and 20 mg/kg) and an oral (20, 50, and 100 mg/kg) administration to rats. The hepatic, gastric, and intestinal first-pass effects were also measured after iv, intraportal (ip), intragastric (ig), and intraduodenal (id) administration at a dose of 20 mg/kg to rats. The areas under the plasma concentration벼ime curve from time to zero to time infinity (AUCs) were independent of iv and oral dose ranges studied; the dose-normalized AUCs were 83.0-104 ? ?min/mL (based on 5 mg/kg) and 78.4-96.8 ? ?min/mL (based on 20 mg/kg) for iv and oral administration, respectively. After an oral administration at a dose of 20 mg/kg, approximately 3% of oral dose was not absorbed and the extent of absolute oral bioavaliability (F) was estimated to be 18.8%. The AUCs of KR-60436 after ig and id administration at a dose of 20 mg/kg were significantly smaller (82.4 and 57.5% decrease, respectively) than that after an ip administration at a dose of 20 mg/kg, suggesting that gastrointestinal first-pass effect of KR-60436 was approximately 80% of oral dose in rats (the gastric first-pass effect was approximately 25%). After an ip administration at a dose of 20 mg/kg, the AUC was 77.6% of an iv administration, suggesting that hepatic first-pass effect was approximately 22% of KR-60436 absorbed into the portal vein. Note that the value of 22% was equivalent to approximately 4% of oral dose. Since only 17% of oral dose was absorbed into the portal vein, the low F of KR-60436 in rats was mainly due to considerable gastrointestinal first-pass effect, approximately 80% (the gastric first-pass effect was approximately 25%) of oral dose.

[PE2-16] [04/18/2003 (Fri) 09:30 - 12:30 / Hall P]

BIOEQUIVALENCE EVALUATION OF FLUCONAZOLE 50 MG THREE CAPSULES IN HEALTHY MALE KOREAN VOLUNTEERS

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The purposes of this study were to evaluate bioequivalence (BE) using ln-transformed pharmacokinetic parameters obtained from two fluconazole products and to develop the analytical methods for the quantitative determination of fluconazole in human serum. In addition, the in vitro dissolution profiles of the two fluconazole products at dissolution media: 0.1 M hydrochloride (KP Ⅶ Apparatus Ⅱ method) were assessed. BE was evaluated in 20 healthy male Korean volunteers in randomized crossover study. Single oral dose of 150 mg of each product was administered after overnight fasting. Blood samples were collected at predetermined time intervals and the concentrations of fluconazole in serum were determined using HPLC method with UV detection. The dissolution profiles of two fluconazole capsules were very similar. Besides, the pharmacokinetic parameters such as AUCt, Cmax and Tmax were calculated and ANOVA test was utilized for the statistical analysis of the parameters using logarithmically transformed AUCt, Cmax and untransformed Tmax. The results showed that the differences in AUCt, Cmax and Tmax between two capsules based on the Diflucan® were 4.96%, 5.65% and -13.76%, respectively. And also, the 90% confidence intervals were within the acceptance range of log(0.8) to log(1.25) (e.g., 1.01~1.08 and 1.00~1.12 for AUCt and Cmax, respectively). Consequently, all parameters met the criteria of KFDA guideline for bioequivalence, indicating that Flucona capsule is bioequivalent to Diflucan® capsule.

[PE2-17] [04/18/2003 (Fri) 09:30 - 12:30 / Hall P]

Improved Dissolution Characteristics of Silymarin and Their Bioavailability in Human Volunteers

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Silybin is the main component of *Cardus marianus* extracts (Silymarin) originated from Silybum marianum, called as milk thistle. It has a hepato-protective effect and is used clinically for the treatment of liver disease. But it is water-insoluble and is poorly absorbed from the gastrointestinal tract, resulting in very low oral bioavailability. Polymeric mixed-micelle precursor formulation containing surfactants, co-solvents, and block-co polymers with *Cardus marianus* extracts was made to enhance the dissolution rate of silybin and encapsulated with soft gelatin capsule. This precursor formulation forms micelle spontaneously when it contacts with gastro-intestinal fluid, and thereby can be absorbed rapidly. The oral bioavailability of the new formulation was estimated in twelve healthy male volunteers, and compared with that of a marketed product. After oral administrations of two capsules at a dose of 120 mg/kg as silybin, pharmacokinetic parameters including Cmax, Tmax, and AUC were obtained from the plasma concentration-time profiles of silybin : Cmax and $AUC_{0\sim8hrs}$ of the new formulation were 4.3 times and 2.4 times greater, respectively, than those of a marketed product.

[PE2-18] [04/18/2003 (Fri) 09:30 - 12:30 / Hall P]

Dose-Independent Pharmacokinetics of a New Neuroprotective Agent for Ischemia-Reperfusion Damage, KR-31543, after Intravenous and Oral Administration to Rats: