

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 μ g) 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 concentration-time 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 bioavailability (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.

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