administration of the same total dose of torasemide at a dose of 1 mg/kg to rabbits with different infusion times, 1 min (treatment I), 30 min (treatment II), and 2 h (treatment III). The loss of water and electrolytes in urine induced by torasemide was immediately replaced with infusion of equal volume of lactated Ringer···s solution. All of the pharmacokinetic parameters of torasemide were independent of infusion times. For example, the mean values of terminal half-life (13.3, 13.7, and 15.8 min for treatments I쩃III, respectively), total area under the plasma concentration쩃time curve from time zero to time infinity (108, 74.4, and 101 꺷g min/ml), total body clearance (9.30, 13.4, and 10.0 ml/min/kg), and apparent volume of distribution at steady state (117, 181, and 148 ml/kg) were not significantly different among three treatments. However, 8-h urine output (235, 534, and 808 ml) and 8-h urinary excretion of sodium (24.2, 80.1, and 89.2 mmol) and chloride (27.1, 89.2, and 94.0 mmol) were significantly greater in treatments II and III than those in treatment I although the total amount of 8-h urinary excretion of unchanged torasemide (1210, 1210, and 1310 꺷g) were not significantly different among three treatments. This could be due to the higher diuretic efficiencies in treatments II and III.

[PE2-13] [04/18/2003 (Fri) 09:30 - 12:30 / Hall P]

Determination of a histone deacetylase inhibitor SD-2007 by LC/MS and application to a pharmacokinetic study in rats

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SD-2007 ia an apicidin analogue, possessing a potent histone deacetylase inhibiting activity. A rapid and senstive LC/MS method was developed for the determination of SD-2007 and its major active metabolite, apicidin, in rat serum. SD-2007 and apicidin was extracted by liquid-liquid extraction using methyl t-butyl ether. SD-2007 and apicidin were monitored in a SIM mode at m/z of 679 and 622, respectively. The chromatographic run time was 7 min and the limit of quantitation was 1 ng/ml for both SD-2007 and apicidin. This method was applied to a pharmacokintic study after i.v. (8 and 12 mg/kg doses) and oral (40 mg/kg dose) administration of SD-2007 in rats. The t1/2 and Vss ranged from 34.9-35.4 min and 3.1-3.4 L/kg, respectively, for SD-2007, and these values were similar to those found for apicidin. The absolute oral bioavailability of SD-2007 was low (2.0 ± 1.7%). However, AUC and Cmax values of the active metabolite, apicidin, were >27-fold greater than those of the parent compound.

[PE2-14] [04/18/2003 (Fri) 09:30 - 12:30 / Hall P]

Effects of the rate and composition of fluid replacement on the pharmacokinetics and pharmacodynamics of intravenous torasemide

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The effects of differences in the rate and composition of intravenous fluid replacement for urine loss on the pharmacokinetics and pharmacodynamics of torasemide were evaluated using rabbits as the animal model. Each rabbit received 2-h constant intravenous infusion of 1 mg kg 쩃1 of torasemide with 0% replacement (treatment I, n = 6), 50% replacement (treatment II, n = 9), and 100% replacement with lactated Ringer's solution (treatment III, n = 8) as well as with 100% replacement with 5% dextrose in water (D-5-W, treatment IV, n = 6). Total body (4.53,

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