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,