A high-performance liquid chromatographic method was developed for the determination of KR-31543 in rat plasma and urine. The retention time of KR-31543 was approximately 3.5 min. The detection limits of KR-31543 in rat plasma and urine were both 200 ng/ml. KR-31543 was relatively stable in various pH (3-13) solutions, and rat plasma and urine for up to 24-h incubation, however, it was unstable in pH 2 solution. KR-31543 reached an equilibrium fast between plasma and blood cells of rabbit blood and the plasma-to-blood cells concentration ratios were independent of initial blood concentrations of KR-31543, 2, 5, and 10 μg/mL, the values were 0.805–1.22. The protein binding of KR-31543 at 4% human serum albumin was 75.2% using an equilibrium dialysis technique. The dose-independent pharmacokinetic parameters of KR-31543 were evaluated after intravenous and oral administration, 10, 20, and 50 mg/kg, to rats. After intravenous administration, the dose-normalized (10 mg/kg) AUC values were comparable among three doses (448–456 μg min/mL). After oral administration, the dose-normalized (10 mg/kg) AUC values were also comparable among three doses (125–176 μg min/mL).

[PE2-6] [10/19/2001 (Fri) 09:00 - 12:00 / Hall D]

Subacute Toxicities and Toxicokinetics of a New Erectogenic, DA-8159, After Single and 4-Week Repeated Oral Administration in Dogs

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The subacute toxicities and toxicokinetics of a new erectogenic, DA-8159, were evaluated after single (at the 1st day) and 4-week (at the 28th day) oral administration of the drug, in doses of 0 (to serve as a control), 12.5, 50, and 200 mg/kg/day, to male and female dogs (n = 3 for male and female dogs for each dose). DA-8159 had an effect on the immune-related organs (or tissues), circulatory systems, liver, adrenal glands, ovaries, and pancreas. The toxic dose was 200 mg/kg and no observed adverse effect level was less than 50 mg/kg for male and female dogs. There were no significant gender differences in the pharmacokinetic parameters of DA-8159 for each dose after both single and 4-week oral administration. The pharmacokinetic parameters of DA-8159 were dose-independent after single oral administration, the time to reach a peak plasma concentration (Tmax) and the dose-normalized area under the plasma concentration-time curve from time zero to 24 h in plasma (AUC0-24 h) were not significantly different among three doses. However, accumulation of DA-8159 after 4-week oral administration was considerable at toxic dose, 200 mg/kg/day. For example, after 4-week administration, the dose-normalized AUC0-24 hvalue at 200 mg/kg/day (4.71 and 15.3 μg h/mL) was significantly greater than that at 12.5 mg/kg/day. After 4-week oral administration, the dose-normalized Cmaxand AUC0-24 h at 200 mg/kg/day were significantly higher and greater, respectively, than those after a single oral administration.

[PE2-7] [10/19/2001 (Fri) 09:00 - 12:00 / Hall D]

Importance of Plasma Globulin Binding of Azosemide for Diuretic Effects in Analbuminemic Rats

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The importance of plasma protein binding of intravenous furosemide in circulating blood for its urinary excretion and hence its diuretic effects in mutant Nagase analbuminemic rats (NARs, an animal model for hypoalbuminemic patients) has been reported. This study reports the importance of globulin binding