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

Shim HyunJoo[o12], Lee EunJu[1], Kim JungHoon[2], Kim SoonHoe[2], Kwon JongWon[2], Kim WonBae[2], Cha Shin-Woo[3], and Lee MyungGull[1]

[1]College of Pharmacy and Research Institute of PharmaceuticalSciences, [2]Research Laboratory, Dong-A Pharmaceutical Company,[3]Toxicology Research Center, Korea Research Institute of Chemical Technology

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

Kim EunJung[oo1], Lee AeKyung[1], Kim SoHee[2], Kim Sang Geon[1], Lee Myung Gull[1]

[1]College of Pharmacy and Research Institute of Pharmaceutical Sciences, Seoul National University, [2]College of Dentistry and Research Institute of Stomatology, Kangnung National University

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

of intravenous azosemide in circulating blood for diuretic effects in NARs. The plasma protein binding of azosemide in control rats and NARs were 97.9 and 84.6%, respectively. The binding values of azosemide to rat α- and β-globulins were 82.6 and 68.9%, respectively, at α- and β-globulin concentrations equivalent to those in plasma of NARs. The percentage of intravenous dose of azosemide excreted in 8-h urine as unchanged diuretic was significantly greater in NARs (37.7 versus 21.0%) and this resulted in a significantly greater 8-h urine output in NARs (385 versus 221 mL/kg). In NARs, the AUC of azosemide was significantly smaller (505 versus 2790 mg min/mL). This could be due to significantly faster CLr (7.36 versus 0.772 mL/min/kg, because of significant increase in intrinsic renal active secretion) and CLnr (12.4 versus 3.05 mL/min/kg, because of approximately 3.5 folds increase in CYP1A2 in rats) than those in control rats. The renal sensitivities to azosemide were significantly greater in NARs than those in control rats in terms of 8-h urine output and 8-h urinary excretions of sodium, potassium,and chloride. This study supports the importance of binding of intravenous azosemide to α- and β-globulins in circulating blood for its diuretic effects.

[PE2-8] [10/19/2001 (Fri) 09:00 - 12:00 / Hall D]

HPLC Analysis, Stability, Blood Partition, and Protein Binding of an Antifibrotic Agent, Oltipraz

Bae SooKyung○[1], Bu SeongChull[1], Kim EunJung[1], Kim SoHee[2], Kim SangGeon[1], and Lee MyungGull[1]

[1]College of Pharmacy and Research Institute of Pharmaceutical Sciences, Seoul National University,[2]College of Dentistry and Research Institute of Stomatology, Kangnung National University

A high-performance liquid chromatographic method was developed for the determination of Oltipraz in rat plasma and urine. The sample preparation was simple, 2 volumes of acetonitrile were added to deproteinize the biological sample. A 50-μl aliquot of the supernatant was injected onto a C_{18} reversed-phase column. The mobile phase, acetonitrile : 0.5 mM ammoniun acetate (55 : 45, v/v for rat plasma and 45 : 55, v/v for rat urine), was run at a flow-rate of 1.5 mL/min. The column effluent was monitored using an ultraviolet detector set at 305 nm. The retention times for Oltipraz in rat plasma and urine were approximately 5.8 and 8.6 min, respectively. The detection limits of Oltipraz in rat plasma and urine were 20 and 50 ng/mL, respectively. Oltipraz was relatively stable in various pH (1-12) solutions for up to 48-h incubation, however, it was unstable in pH 13 solution and rat plasma and urine. Oltipraz reached an equilibrium fast (within 30 s mixing manually) between plasma and blood cells of rabbit blood and the plasma-to-blood cells concentration ratios were independent of initial blood concentrations of Oltipraz, 1 and 5 μ
g/mL, the ratios ranged from 0.908 to 1.004. The binding of Oltipraz to 4% human serum albumin (HSA) was independent of Oltipraz concentrations ranging from 1 to 100 μg/mL using an equilibrium dialysis technique: the mean value was 95.0%. However, the binding of Oltipraz was dependent on HSA concentrations and the buffer pHs.

[PE2-9] [10/19/2001 (Fri) 09:00 - 12:00 / Hall D]

Pharmacokinetics and Pharmacodynamics of Intravenous Bumetanide in Mutant Nagase Analbuminemic Rats: Importance of Globulin Binding for the Pharmacodynamic Effects

Kim EunJung○, and Lee MyungGull

College of Pharmacy and Research Institute of Pharmaceutical Sciences, Seoul National University

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 was reported. Based on the furosemide report, the diuretic effects of another loop diuretic, bumetanide, could be expected in analbuminemic rats if plasma protein binding of bumetanide is considerable in the rats. This was proved by this study. After intravenous administration of bumetanide, 10 mg/kg, to analbuminemic rats, the