The correlations between various factors (such as sex, age, height, weight, serum creatinine (Scr) and dose) and pharmacokinetic parameters were estimated with stepwise linear regression analyses. The selected covariates were incorporated in the population model of NONMEM program and the importance of each covariate was investigated by means of backwards elimination.
The apparent clearance (CL/F) was significantly correlated to Scr and sex, and the apparent volume of distribution (V/F) was significantly correlated to Scr and height in a nonlinear relationship. The population values of Ka was 1.8 hr-1, CL/F was 37.71 L/hr, V/F was 200 L and t1/2 was 3.68 hrs for a male Korean with 170 cm height and 1.0 mg/dL Scr.
It is considered to have wider range of subjects to improve the population model of clarithromycin.

[PE2-4] [ 10/19/2001 (Fri) 09:00 - 12:00 / Hall D ]

## Metabolism study of CKD-732, a novel anti-angiogenic fumagillin derivative, with in vitro rat hepatic microsome and rat plasma, urine and bile.

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CKD-732 (4-O-[4-(dimethylaminoethoxy)cinnamoyl]fumagillol) under development as an antiangiogenic and antitumor agent has been expected to include several metabolic sites that can be attacked by metabolic enzymes. In order to elucidate the metabolic patterns and pathway of CKD-732, its metabolites from *in vitro* rat hepatic microsome and rat plasma, urine and bile were analyzed by UV-VIS and MS. In addition, we purified the major one (M11) of the metabolites and identified its chemical structure by NMR.
The parent and fourteen metabolites were found from the *in vitro* samples, which were separated by HPLC and subsequently identified by Ion-trap MS. Full scan mass spectrum of CKD-732 gave an intense pseudo-molecular ion $[M+H]^+$ at m/z 500 and potassium additive ion $[M+K]^+$ at m/z 538. The major metabolite (M11, $[M+H]^+$ m/z 516) eluted later than the parent by HPLC was identified as the N-oxide form of CKD-732. In contrast to the *in vitro* profiles, only two metabolites were found in rat plasma and the N-oxide form of CKD 732 was also the major metabolite detected with comparable peak area to that of the parent. In urine and bile, CKD-732 was also metabolized into about twenty four metabolites by oxidase, hydroxylase, demetylase and hydrolase, following intravenously administration. Among them, ten and thirteen metabolites in each sample covered >1% of total ion peak area, the metabolic patterns of which were almost identical with that of fourteen metabolites in *in vitro*. And it was found that the N-oxide form in bile was also detected as the major metabolite but not in urine. The current results show that the major metabolic pathway of CKD-732 is associated with N-oxidation in the liver.

[PE2-5] [ 10/19/2001 (Fri) 09:00 - 12:00 / Hall D ]

## HPLC Analysis, Stability, Blood Partition, Protein Binding, and Dose-independent Pharmacokinetics of KR-31543, a New Neuroprotective Agent for Ischemia-reperfusion Damage

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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