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.

LEE HO SUP°, KIM HYE YOUNG[1], SOHN YOUNG SUNG, CHOI WON KYU, SON HOE JOO, LEE SUNGSOOK, MYUNG SEUNG WOON[1], KIM JOON-KYUM, AHN SOON KIL, HONG CHUNG IL

CKD Research Institute, Chonan P.O. Box 74, Chonan 330-600, Korea and Doping control center, Korea Institute of Science and Technology, P.O. Box 131, Cheongryang, Seoul, 130-650, Korea[1].

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

Lee MiHye°°[1], Kim EunJung[1], Kim YoonGyoon[1], Kim Sun-Ok[2], Lee Dong-Ha[2], Lim Hong[2], Yoo Sung-Eun[3], and Lee Myung Gull[1]

[1]College of Pharmacy and Research Institute of Pharmaceutical Sciences, Seoul National University, [2]AgroPharma Research Institute, Dongbu Hannong Chemical Company, [3]Korea Research Institute of Chemical Technology