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The purposes of this study were to assess the pharmacokinetics of aceclofenac in Korean using a population approach and to investigate the influence of characteristics of subjects such as body weight and age on that of aceclofenac. Plasma data from 156 Korean healthy male subjects who participated in several different bioequivalence studies of aceclofenac 100 ㎎ were used for this analysis. Plasma aceclofenac concentrations were measured using HPLC with UV detector. A 2-compartment model with lag time was fitted to the aceclofenac data using NONMEM. In result, population mean Cl/F, V_c/F, K_a, V_p/F, Q/F and T_{lag} were 4.37×10^3 ㎖/hr, 3.95×10^3 ㎖, 0.99 hr^{-1}, 9.60×10^3 ㎖, 1.02×10^3 ㎖/hr and 0.39 hr, respectively. Intersubject coefficient of variation (CV) ranged from 0.06 to 74.90% and residual intrasubject CV was 40.50%. A 2-compartment model with lag time was fitted well to the aceclofenac data, and there were no influence of age or body weight on fitting.

[PE2-2] [10/19/2001 (Fri) 09:00 - 12:00 / Hall D]

Validation of a high-performance liquid chromatographic method for the determination of YH3945 in rat plasma

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YH3945, a non-peptide farnesyltransferase inhibitor, is being developed by Yuhan Research Institute for the treatment of cancer. A sensitive and specific assay based on high perfomance liquid chromatography (HPLC) has been developed and validated for the determination of YH3945 in rat plasma. Plasma was extracted with acetonitrile containing the internal standard. An aliquot of the extract was injected onto a reverse C18 column. Retention times of YH3945 and the internal standard were 6.25 and 9.94 min, respectively. The chromatograms showed no endogenous peaks from blank plasma at the retention time of YH3945. Standard curves of YH3945 was linear over the range of 50 ng/ml to 5000 ng/ml (r=0.9998). The lower limit of quantification was 50 ng/ml using 100 ul plasma. This assay also showed good inter- and intra-precision and accuracy throughout the concentration range. YH3945 was stable for 72 hours in the sample extract, for 4 hours in ambient condition, for up to 14 days at frozen condition, and after exposure to three freeze/thaw cycles. This sensitive, accurate and precise method can be applied to determine concentration of YH3945 in plasma for pharmacokinetic studies in rats.

[PE2-3] [10/19/2001 (Fri) 09:00 - 12:00 / Hall D]

Population pharmacokinetics of clarithromycin in healthy adult Korean

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The purpose of this study is to estimate the population pharmacokinetics of clarithromycin in healthy adult Korean and to investigate the influence of various factors on the pharmacokinetics of clarithromycin.
The population pharmacokinetic parameters of clarithromycin were calculated with the data from the bioequivalance test. A total of 798 plasma concentrations from 78 subjects with single oral dose of 250mg or 500mg were used for the modeling. The concentration-time data were fitted to one-compartment open model with first-order absorption and elimination with no lag time using WinNonlin.

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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