in plasma. The precision and accuracy was found to be satisfactory over the whole range tested (0.5 ~ 50 ng/ml). This method was applied to human plasma samples from 8 healthy volunteers after oral administration of 20 mg of loratadine as tablets. Blood was collected up to 24 hours after dosing. Loratadine was rapidly absorbed following oral administration, with mean $C_{\text{max}}$ of 18.25 ng/mL within 0.67 ~ 1.0 hr (mean $T_{\text{max}}$: 0.92 hr). The AUC, $k$ and $t_{1/2}$ of loratadine were 30.51 ng/hr/mL, 0.6182 hr$^{-1}$ and 1.22 hr, respectively.

**POPULATION PHARMACOKINETICS OF TERBINAFINE IN HEALTHY MALE KOREAN SUBJECTS USING NONMEM**

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The purposes of this study were to evaluate the population pharmacokinetics of terbinafine according to two-compartment model with lag time and to investigate the influence of characteristics of subjects such as body weight and age on the pharmacokinetic parameters of terbinafine. Serum data from 73 healthy male Korean subjects were used for this analysis. After overnight fast, each subject received a single 125 mg oral dose of terbinafine. Serum concentrations of terbinafine were measured using HPLC with UV detection. A two-compartment model with lag time was fitted to the terbinafine data using NONMEM. Population mean CI/F, V/F, $K_{\text{a}}$, $V_{\text{p}}$/F, Q/F and $T_{\text{lag}}$ were $5.20 \times 10^4$ ml/hr, $1.22 \times 10^4$ ml, 0.50 hr$^{-1}$, $4.39 \times 10^5$ ml, $2.55 \times 10^4$ ml/hr and 0.43 hr, respectively. Intersubject coefficient of variation (CV) ranged from 13.25 to 41.37% and residual intra-subject CV was 34.43%. A two-compartment model with lag time was well fitted to the terbinafine data, and there were no influences of age, body weight, height and serum creatinine concentration on fitting.

**Kinetic Characterization of Brain Distribution for KR-31378 in Rats**

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Recent studies show that KR-31378 [(2S,3S,4R)-N-(4-cyano-N-[6-amino-3,4-dihydro-3-hydroxy-2-methyl-2-dimethylaminoethyl-2H-benzopyran-4-yl]-N-+-benzoylguanidine] has the neuroprotective effect as evidenced by the limitation of the size of infarct of the ischemia–reperfusion injury after an administration of KR-31378. In the literature, however, kinetics of KR-31378 distribution into the brain has not been systematically studied. To determine the kinetics of the drug in the rat brain, blood and brain samples were collected at 1, 5, 30, 60, 120, and 240 min after an intravenous administration 10 mg and 50 mg of KR-31378/kg rat, and the concentration in these biological samples assayed by a HPLC method. The brain concentrations of KR-31378 were found to be approximately 10~20-fold lower than those of plasma, indicating that slow influx and/or rapid efflux of the drug across the blood brain barrier may occur. Kinetic analysis of uptake for KR-31378 into rat brain revealed that the net uptake clearance increased by 2.21-fold with an increase in dose (7.33 ± 0.0897 ml/min for 10 mg/kg vs. 16.2 ± 5.19 ml/min for 50 mg/kg; p<0.05). This finding suggests that an efflux system is involved in the penetration of KR-31378 across the blood–brain barrier and that the presence of an efflux system for the drug may be responsible for the low brain concentration of KR-31378. Intravenous pretreatment of KR-30031a, a multidrug resistance (MDR) activity modulator, was found to enhance the brain/plasma ratio for KR-31378 by 2.43-fold (10 mg/kg) and 1.92-fold (50 mg/kg), indicating that MDR transporter mediates the efflux of KR-31378 across the blood brain barrier. Taken together, these results suggest that MDR transporter may be responsible, at least in part, for the efflux of KR-31378 across the blood brain barrier, thereby limiting the concentration of the drug in the brain.

**PK/PD modeling for cardiovascular effect of carvedilol in healthy volunteers**

[PE2-6] [10/18/2002 (Fri) 13:30 - 16:30 / Hall C]