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_{max} of 18.25 ng/mL within 0.67 ~ 1.0 hr (mean T_{max} : 0.92 hr). The

AUC, k and $t_{1/2\beta}$ of loratadine were 30.51 ng·hr/mL, 0.6182 hr^{-1} and 1.22 hr, respectively.

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

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 ㎎ 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 Cl/F, V_c/F,

K_a, V_p/F, Q/F and T_{lag} were 5.20×10^4 ㎖/hr, 1.22×10^4 ㎖, 0.50 hr^{-1}, 4.39×10^5 ㎖, 2.55×10^4 ㎖/hr and 0.43 hr, respectively. Intersubject coefficient of variation (CV) ranged from 13.25 to 41.37% and residual intrasubject CV was 34.43%. A two-compartment model wth 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.

[PE2-7] [10/18/2002 (Fri) 13:30 – 16:30 / Hall C]

Kinetic Characterization of Brain Distribution for KR-31378 in Rats

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Recent studies show that KR-31378 [(2S,3S,4R)-N ″ -cyano-N-(6-amino-3,4-dihydro-3-hydroxy-2-methyl-2-dimethoxymethyl-2H-benzopyran-4-yl)-N ⋯ -benzylguanidine] 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 ㎕/min for 10 mg/kg vs. 16.2 ± 5.19 ㎕/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.

[PE2-8] [10/18/2002 (Fri) 13:30 – 16:30 / Hall C]

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

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Carvedilol is a nonselective β-adrenoblocking agent with vasodilating activities. The pharmacokinetics and pharmacodynamics of carvedilol were studied in healthy volunteers following single oral administration. After oral administration of carvedilol 25mg, blood samples were collected for a period of 30 hours. Plasma concentrations of carvedilol were determined by HPLC with spectrofluorometric detection. The effects of carvedilol on systolic and diastolic blood pressure (BP) and heart rate (HR) were measured during the same period. The time courses of the plasma concentration of carvedilol and the cardiovascular effects (BP and HR) were analyzed with PK/PD modeling using ADAPT II program.

The estimated Cmax, Tmax, CL/F(apparent clearance), V/F(apparent volume of distribution) and half-life of carvedilol were 66.43±2.86 ng/L, 1.13±0.08 hrs, 92.26±5.32 L/hr, 663.31±34.10 L, and 5.48±0.24 hr, respectively. The maximal decrease in SBP was 11.70% and in DBP was 28.89% at and in HR was 15.22%. Both the maximum change in SBP and HR were detected at 3hr after administration of the drug. But the maximum change in DBP were observed at 6hr. Direct response model was tested for the change in SBP, DBP and HR. Plasma drug concentrations were linked to the observed effects via an effect compartment model with a sigmoid Emax model. These PK/PD model could describe the relationship between carvedilol plama concentration and cardiovascular effects.

[PE2-9] [10/18/2002 (Fri) 13:30 - 16:30 / Hall C]

Pharmacokinetic Scaling of SJ-8029, a Novel Anticancer Agent Possessing Microtubule and Topoisomerase Inhibiting Activities, by Species-Invariant Time Methods

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This study examined the pharmacokinetic disposition of SJ-8029, a novel anticancer agent possessing microtubule and topoisomerase inhibiting activities, in mice, rats, rabbits and dogs after i.v. administration. The serum concentration-time curves of SJ-8029 were best described by tri-exponential equations in all these animal species. The mean Cl, V_{ss} and $t_{1/2}$ were 0.3 L/h, 0.1 L and 63.2 min in mice, 1.5 L/h, 1.6 L and 247.7 min in rats, 13.8 L/h, 39.6 L and 245.9 min in rabbits, and 29.2 L/h, 44.6 L and 117.4 min in dogs, respectively. Based on animal data, the pharmacokinetics of SJ-8029 were predicted in humans using simple allometry and also by several species-invariant time transformations using kallynochron, apolysichron and dienetichron times. The species-invariant time transformations showed that all animal data from four species were superimposable. The human pharmacokinetic parameters of Cl, V_{ss} and $t_{1/2}$ predicted by the simple allometry and various species-invariant time methods ranged from 50.4-145.0 L/h, 369.0-579.8 L and 242.0-1448.3 min, respectively. These preliminary parameter values may be useful in designing early pharmacokinetic studies of SJ-8029 in humans.

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

Kinetic Analysis of the Hepatic Uptake and Biliary Excretion of IH-901, a Potential Anticancer Agents, in Rats

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The purpose of the present study was to investigate the hepatic uptake and biliary excretion of IH-901, a potential anticancer agents, in rats. IH-901 was mainly distributed into the liver after its iv administration at the dose of 10-30 mg/kg. The liver concentration of IH-901 at 7 min after its iv administration was comparable with its initial concentration of the plasma. Moreover, recovery ratio of IH-901 in the bile for 6 hr was more than 40% after its iv administration. The early phase (0-5 min) of the plasma concentration was disappeared by exponentially. The hepatic recovery ratio (Rh) was estimated by comparing the liver concentration and that disappeared from the circulation. The Rh value was about more than 30%, indicating that the liver is one of the