

under different agitation conditions. The permeabilities of some hydrophobic drugs were increased when measured under accelerated agitation. Thus, we studied whether the agitation speed affects the permeability of certain drugs. Then we studied whether there are any relationships between the difference in Papp by the agitation ( $\Delta$ Papp) and the hydrophobicity of drugs. Finally, we investigated the effect of agitation on the predictability of *in vivo* bioavailability of a drug from *in vitro* permeability of the drug across Caco-2 cell monolayers. The transport of drugs across Caco-2 cell monolayers were examined under two different conditions (60 rpm agitation and no agitation) using a plate shaker. Permeability (Papp) of propranolol, YH439 and phenylpropanolamine were slightly increased by the 60rpm agitation. But, Papp of mannitol, TBuMA, cimetidine, ranitidine, hydrocortisone, theophylline, benzylpenicillin and loxoprofen were not affected by the agitation. There is no significant relationship between the  $\Delta$ Papp and hydrophobicity of drugs. In addition, the agitation did not change the relationship between the permeability and the bioavailability of drugs. Agitation did not affect the correlation between *in vitro* permeability across Caco-2 cells and *in vivo* bioavailability of drugs. Thus, it could be concluded that agitation during the determination of permeabilities of drugs does not affect the practical predictability. It may not be necessary to consider the effect of agitation in predict *in vivo* bioavailability of xenobiotics from the permeability of the compounds across Caco-2 cell monolayers

[PE2-4] [ 10/18/2002 (Fri) 13:30 - 16:30 / Hall C ]

#### BIOEQUIVALENCE EVALUATION OF TIROPRAMIDE HCl 100 MG TABLETS IN HEALTHY MALE KOREAN VOLUNTEERS

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The purposes of this study were to evaluate bioequivalence (BE) using *In*-transformed pharmacokinetic parameters obtained from two tiropamide HCl products and to develop the analytical methods for the quantitative determination of tiropamide in human serum. In addition, the *in vitro* dissolution profiles of the two tiropamide HCl products in various dissolution media: pH 1.2, 4.0, 6.8 and water (KP VII Apparatus II method) were assessed. BE was evaluated in 20 healthy male Korean volunteers in randomized crossover study. Single oral dose of 100 mg of each product was administered after overnight fasting. Blood samples were collected at predetermined time intervals and the concentrations of tiropamide in serum were determined using column-switching HPLC method with fluorescence detection. The dissolution profiles of two tiropamide HCl tablets were very similar at all dissolution media. Besides, the pharmacokinetic parameters such as AUCt, Cmax and Tmax were calculated and ANOVA test was utilized for the statistical analysis of the parameters using logarithmically transformed AUCt, Cmax and untransformed Tmax. The results showed that the differences in AUCt, Cmax and Tmax between two tablets based on the Tiropa were -6.51%, -2.93% and 4.69%, respectively. And also, the 90% confidence intervals were within the acceptance range of log(0.8) to log(1.25) (e.g., 0.84~1.02 and 0.89~1.03 for AUCt and Cmax, respectively). Consequently, all parameters met the criteria of revised KFDA guideline for bioequivalence, indicating that Tiroma tablet is bioequivalent to Tiropa tablet.

[PE2-5] [ 10/18/2002 (Fri) 13:30 - 16:30 / Hall C ]

#### HPLC Determination of Loratadine in Human Plasma with UV Detection and Pharmacokinetics of Loratadine Following Oral Administration of Tablet Formulation in Human

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A validated UV determination of loratadine in human plasma was developed and the pharmacokinetic profiles of single dose of loratadine were determined in 8 healthy volunteers. Human serum samples (1.0 mL) spiked with known concentration of loratadine and 50 ng diazepam as an internal standard were alkalized with 500  $\mu$ l of 10% Na<sub>2</sub>CO<sub>3</sub> and extracted with 7 mL of mixture of isopentane and hexane (2 : 1, v/v) for 5 min. Extracts were centrifuged and 6 mL of organic layer was back-extracted with 150  $\mu$ l of 12.5% H<sub>3</sub>PO<sub>4</sub> for 1 min. One hundred microliters of centrifuged aqueous layer were injected onto reversed-phase octadecyl column and eluted with a mixture of acetonitrile, water, NH<sub>4</sub>H<sub>2</sub>PO<sub>4</sub> and phosphoric acid (43 : 57 : 0.6 : 0.3, v/v/w/v) at a flow rate of 1.5 mL/min. UV detection was performed at 200 nm with a limit of quantification of 0.5 ng/mL. The calibration curve obtained using peak area ratios showed a good linearity ( $r^2 = 0.9991$  in the concentration range 0.5 ~ 50 ng/mL

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<sup>-1</sup> 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 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  $Cl/F$ ,  $V_c/F$ ,  $K_a$ ,  $V_p/F$ ,  $Q/F$  and  $T_{lag}$  were  $5.20 \times 10^4$  mL/hr,  $1.22 \times 10^4$  mL,  $0.50$  hr<sup>-1</sup>,  $4.39 \times 10^5$  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 intrasubject 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.

[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 ( $7.33 \pm 0.0897$   $\mu$ L/min for 10 mg/kg vs.  $16.2 \pm 5.19$   $\mu$ L/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