spectrometer.

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Enalapril, a prodrug, is the ethyl ester of a long-acting angiotensin converting enzyme inhibitor, enalaprilat. Because enalapril does not contain any appreciable chromophore, detection of the drug in a complex matrix (e.g., biological fluids) has been problematic with conventional detection systems in high-performance liquid chromatography (HPLC). As a result, determination of enalapril level in blood samples has been typically carried out using HPLC-MS/MS in the literature. Since availability of HPLC-MS/MS has been significantly limited, we studied the feasibility of using HPLC-MS, a more widely equipped instrument, for the determination of the drug in human blood samples. In this study, C18 reversed phase column (column temperature of 40 ℃) was used as a stationary phase. Mobile consisted of acetonitrile and formate buffer (1:3, pH 3) with a flow rate of 0.2 ml/min. For the detection enalapril, m/z value was fixed at 377.2. Deproteinating agents (Acetonitrile 100 ㎕, $ZnSO_4$ 10%) were added to human blood sample (i.e., 200 ㎕); Resulting mixture was vortex-mixed and the supernatant collected. Then, an aliquot (5 ㎕) of the supernatant was directly injected on to the HPLC-MS system. Based on the experimental condition, a linear (i.e., r^2=0.9954) correlation between the concentration and the LC-MS response was readily obtained in a concentration range of 3 ~ 225ng of enalapril/ml of human blood using 200 ㎕ blood sample. In addition, variability of the assay was always less than 15 % for precision and accuracy. The limits of detection and quantitation of the method were found to be 1 and 3 ng/ml, respectively. Considering the fact that C_{max} of the drug is approximately 100 ng/ml, the validated HPLC-MS assay has a sufficient sensitivity for the use of pharmacokinetic characterization of enalapril in human subjects (e.g., human bioequivalence trial).

[PE2-2] [10/18/2002 (Fri) 13:30 - 16:30 / Hall C]

The Effect of Nimodipine on the Pharmacokinetics of Cyclosporine in Rabbits

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The purpose of this study was to report the pharmacokinetic changes of cyclosporine after oral administration of cyclosporine, 10 mg/kg, in rabbits coadministered or pretreated twice per day for 3 days with nimodipine, dose of 5 mg/kg. The area under the plasma concentration-time curve (AUC) of cyclosporine was significantly higher in rabbits pretreated with nimodipine than in control rabbits ($p<0.01$), showing about 149% increased relative bioavailability. The peak plasma concentration (Cmax) , elimination half-life (t 1/2) and MRT of cyclosporine were increased significantly ($p<0.05$) in rabbits pretreated with nimodipine compared with those in control rabbits. This findings could be due to significant reduction of elimination rate constant and total body clearance by pretreated with nimodipine. The effects of nimodipine on the pharmacokinetics of oral cyclosporine were more considerable in rabbits pretreated with nimodipine compared with those in control rabbits. The results suggest that the dosage of cyclosporine should be adjusted when the drug would be coadministered chronically with nimodipine in a clinical situation.

[PE2-3] [10/18/2002 (Fri) 13:30 - 16:30 / Hall C]

Does Agitation Condition Affect the Correlation Between in vitro Permeability of Xenobiotics across Caco-2 Cells and in vivo Bioavailability of the Compounds?

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Caco-2 is a cell line derived from the human colon adenocarcinoma and often used as a model for studying intestinal drug absorption. It has been well-known that a strong correlation holds between in vitro permeability across Caco-2 cell monolayers and in vivo bioavailability for various drugs, but the correlation curves varied depending on laboratories. The permeabilities of drugs across Caco-2 cell monolayers have been measured

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 (△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 △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 permeaility across Caco-2 cells and in vivo bioavailabity 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 bioavailabililty 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 ln-transformed pharmacokinetic parameters obtained from two tiropramide HCl products and to develop the analytical methods for the quantitative determination of tiropramide in human serum. In addition, the in vitro dissolution profiles of the two tiropramide 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 tiropramide in serum were determined using column-switching HPLC method with fluorescence detection. The dissolution profiles of two tiropramide 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 alkalinized with 500 ㎕ of 10% Na_2CO_3 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 ㎕ of 12.5% H_3PO_4 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, $NH_4H_2PO_4$ 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