A high-performance liquid chromatographic method was developed for the determination of KR-60436 in human plasma and urine and rat tissue homogenates. The retention time for KR-60436 was approximately 7 min and the detection limits of KR-60436 in human plasma and urine, and rat tissue homogenates (including blood) were 0.05, 0.05, and 0.1 μg/ml, respectively. KR-60436 seemed to be stable in pH solutions of from 1 to 13, rat plasma, urine, and liver homogenate up to 24 h incubation, more than 85% of the spiked amount of KR-60436 were recovered. KR-60436 rapidly reached equilibrium between plasma and blood cells of rabbit blood and the plasma/blood cell partition ratios of KR-60436 were independent of blood KR-60436 concentrations, the mean values were 0.837-1.034 at blood KR-60436 concentrations of 2, 5 and 10 mg/mL. The protein binding of KR-60436 at 4% human serum albumin was 97.5% using an equilibrium dialysis technique. The binding value was dependent of pH, human serum albumin concentration, KR-60436 concentration, and the concentration of salicylic acid and sulfisozoxazole. The dose-independent pharmacokinetic parameters of KR-60436 were evaluated after intravenous (5, 10, and 20 mg/kg) and oral (20, 50, and 100 mg/kg) administrations of the drug to rats. After intravenous administration, the dose-normalized (based on 5 mg/kg) values of area under the plasma concentration-time curve from time zero to time infinity (AUC) were comparable among three doses (83.0-104 μg min/mL). After oral administration, the dose-normalized (based on 20 mg/kg) AUCs were also comparable among three doses (55.9-87.8 μg min/mL).

[PE2-17] [10/19/2001 (Fri) 09:00 - 12:00 / Hall D]

Pharmacokinetics of acebutolol and its main metabolite, diacetolol after oral administration in rabbits pretreated and coadministered with diltiazem

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Acebutolol is almost absorbed after oral administration, but its bioavailability is reduced because of considerable first-pass metabolism through the gastrointestinal tract and liver. The purpose of this study was to report the pharmacokinetic changes of acebutolol (15 ㎎/kg, oral) and its main metabolite, diacetolol in rabbits pretreated (15 ㎎/kg, oral) and coadministered (15 ㎎/kg, S.C., bid for 3 days) with diltiazem. The plasma concentration and area under the plasma concentration-time curves (AUC) of acebutolol and diacetolol were significantly increased in rabbits pretreated and coadministered with diltiazem. The elimination rate constant (Kel) and total body clearances (CLt) of acebutolol and diacetolol were significantly decreased and half-life of those were significantly prolonged in the rabbit. Metabolite percentage rate of diacetolol to the plasma concentration of total acebutolol in rabbits pretreated and coadministered with diltiazem were significantly decreased. The results suggest that the dosage of acebutolol should be adjusted when the drug would be administered chronically with diltiazem in a clinical situation.

[PE2-18] [10/19/2001 (Fri) 09:00 - 12:00 / Hall D]

Enhancing effects of cyclodextrins on the permeability of rhEGF across nasal and ocular epithelia in rabbits

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The purpose of the present study was to screen absorption enhancers for the development of mucosal delivery dosage forms contaning recombinant human epidermal growth factor (rhEGF). The peameability of rhEGF across nasal, cornea and conjuctiva epithelia was determined by Ussing chamber. Six cyclodextrins, absorption enahncers of insulin, were used in the experiment. Enhancing effects of cyclodextrins on the mucosal permeability of polypeptides were known to be mainly due to the interaction of cyclodextrins with lipids or divalent cations on the membrane surface. In addition, sodium

caprate (medium chain fatty acid salts), sodium lauryl sulfate (synthetic surfactant) and sodium tauro-deoxycholate (bile acid salts) were investigated for their possibility of absorption enhancers. The apparent permeability constants of rhEGF across conjuntiva epithelia were 10-20 times higher compared with across nasal membranes. On the other hand, the apparent permeability of rhEGF across cornea was negligible. Enhancing effects on the rhEGF permeability across the nasal and conjuntiva were as the following order: alpha-cyclodextrin = dimethyl-beta-cyclodextrin > sodium-taurodeoxycholate > hydroxypropyl-alpha cyclodextrin > dimethyl-alpha-cyclodextrin > beta-cyclodextrin > hydroxypropyl-beta-cyclodextrin > sodium lauryl sulfate > sodium caprate. The penetrated amount of rhEGF across nasal by 4 hr was less than 1.0%, whereas being increased up to 5% by the addition of alpha-cyclodextrin (α-CD) or dimethyl-beta-cyclodextrin (DM-β-CD). The present results suggest that cyclodextrins, especially DM-β-CD and α-CD may serve as potent absorption enhancers for the nasal delivery of rhEGF.

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

Predicting Pharmacokinetic Parameters of Bisphenol A in Humans from Animals Using Allometric Scaling

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Allometric scaling was used to extrapolate the pharmacokinetic parameters of bisphenol A from animals to humans. Bisphenol A was injected intravenously to mice (2 mg/kg), rats (1 mg/kg), rabbits (1 mg/kg) and dogs (1 mg/kg), and serial blood samples were collected. Serum concentrations of bisphenol A were determined by HPLC with fluorescence detection at excitation and emission wavelengths of 278 and 315 nm. The steady-state volumes of distribution of bisphenol A were 0.1, 1.3, 7.1 and 20.0 L in mice, rats, rabbits and dogs, respectively, and the systemic clearances were 0.3, 1.9, 12.6 and 27.1 L/hr, respectively. A regression of the logarithm of the pharmacokinetic parameter and the body weight produced a linear relationship for these parameters. Using the allometric equation, the values of Cls, Vss, and t1/2 predicted for a 70 kg human were 127.1 L/hr (Cls = 5.264 W0.749), 125.3 L (Vss = 2.994 W0.879), and 43.6 min (t1/2 = 40.723 W0.016), respectively. Based on these values, bisphenol A is expected to be eliminated rapidly from humans, with its elimination occurring via the hepatic as well as other routes.

[PE2-20] [10/19/2001 (Fri) 09:00 - 12:00 / Hall D]

Maternal-Fetal Disposition of Bisphenol A in Pregnant Rats

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This study examined the maternal-fetal disposition of bisphenol A and its distribution into the placenta and amniotic fluid after i.v. injection (2 mg/kg) to pregnant SD rats. Bisphenol A was distributed extensively to the placenta and fetus, but the distribution of bisphenol A into the amniotic fluid was low. The decay curve of bisphenol A in the placenta, fetus and amniotic fluid paralleled that of the maternal serum during the terminal elimination phase. A 5-compartment open model consisting of the maternal central, maternal peripheral, placental, fetal and amniotic fluid compartments was used to describe the disposition of bisphenol A in pregnant rats, with the elimination occurring from the maternal central and fetal compartments. Based on this model, bisphenol A was transferred from the placenta primarily to the fetus (65.4%), with the remaining fraction transported to the maternal central (33.2%) and amniotic fluid (1.4%) compartments. Bisphenol A was eliminated from the amniotic fluid by the fetal (63.9%) and placental (36.1%) routes. On the other hand, bisphenol A was eliminated from the fetus primarily by the placental route back to mother (100%), with the amniotic route playing an insignificant role in the fetal elimination. The pharmacokinetic model used in this study provides insights into the routes of elimination of bisphenol A in the maternal-fetal rat upon maternal administration.