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

Burm JinPil°, Lee JinHwan, Choi JunShik

College of Pharmacy, Chosun University and Chosun Nursing College, Kwangju, Korea

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

Lee KyeWon°, Kim InWha, Moon DongCheul, Chung YounBok

College of Pharmacy, Chungbuk National University, Cheongju, Chungbuk 361-763, Korea

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