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Dehydroevodiamine (DHED) is an experimental new drug candidate that is intended for use in the treatment of Alzheimer's disease. The drug is thought to exert its pharmacological action via cholinesterase inhibition, similar to tacrine and donepezil. The objective of this study is to characterize kinetics of brain distribution for DHED in rats. The drug was intravenously infused (0.2, 0.5, 0.02 mg/min) for 15 min to Sprague-Dawley rats (body weight 280-350 g). At predetermined time, the animal was sacrificed by decapitation and the brain was immediately removed. In addition, trunk blood was collected. The tissue was then weighed and homogenized in 2 fold volume of saline (pH 7.4). The concentration of DHED in the brain homogenate was compared with that in the plasma by an HPLC assay for DHED. In the dose range studied (1 mg/kg-10 mg/kg), temporal profiles of brain DHED concentration was almost identical to those in plasma, indicating that the drug crosses the blood brain barrier by passive diffusion. As a result, brain to plasma concentration ratio (Kd brain) is approximately 1. To determine whether DHED was first transported to the cerebrospinal fluid (CSF) and subsequently to the systemic circulation, temporal profile of DHED concentration in the CSF is also monitored. In all samples collected, CSF concentration of DHED was negligible, indicating that the drug may not be primarily eliminated via the blood-CSF barrier. Therefore, these data indicate that distribution kinetics of DHED from the systemic circulation to the brain is primarily mediated by the passive diffusion in the plasma concentration between 2 and 800 ng/ml

[PE2-15] [10/19/2001 (Fri) 09:00 - 12:00 / Hall D]

Tissue distribution study in nude mice bearig solid lung tumor after administration of thermosensitive drug KBP93804A

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KBP93804A is a developing thermosensitive anti-tumor drug in solid tumors. The platinum distribution of KBP93804A was compared with that of cisplatin in nude mice bearing solid lung tumor after single dose treatment. Various main organs such as liver, lung, heart, brain, tumor, kidney and whole blood were collected at 0.5, 1, 5, 12, 24, 48, 72 hours after intra-tumor administration. After digestion with HNO3 and then H202, Pt was measured with inductively coupled plasma-mass spectrometry(ICP-MS). Platinum concentration at tumor after KBP93804A was significantly higher, whereas this concentration at kidney was much less than those of cisplatin. Based on these results, this novel platinum(II) thermosensitive compound (KBP93804A) represents a valuable lead in the development of a new anticancer chemotherapeutic agent capable of improving antitumor activity and low nephrotoxicity.

[PE2-16] [10/19/2001 (Fri) 09:00 - 12:00 / Hall D]

HPLC Analysis, Stability, Blood Partition, Protein Binding, and Dose-independent Pharmacokinetics of A New Reversible Proton Pump Inhibitor, KR-60436, after Intravenous and Oral Administration to Rats

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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