plasma protein binding of bumetanide was 36.8% in the rats mainly due to considerable binding to α- and β-globulins (this value, 36.8%, was considerably greater than only 12% for furosemide), and hence the percentages of intravenous dose of bumetanide excreted in 6-h urine as unchanged drug was 16.0% in the rat (this value was considerably greater than only 7% for furosemide). After intravenous administration of bumetanide to analbuminemic rats, the AUC (1012 versus 2472 μg min/mL) was significantly smaller [due to significantly faster both CLr (1.49 versus 0.275 mL/min/kg) and CLnr (8.30 versus 3.71 mL/min/kg)], terminal half-life (9.94 versus 22.4 min) and MRT (4.25 versus 5.90 min) were significantly shorter (due to faster CL, 9.88 versus 4.05 mL/min/kg), and amount of 6-h urinary excretion of unchanged bumetanide (559 versus 261 mg, due to increase in intrinsic renal excretion) was significantly greater than that in control rats. The 6-h urine output and 6-h urinary excretions of sodium, chloride and potassium were comparable between two groups of rats.

[PE2-10] [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

Nam KiWon°, Chun SungKuk, Oh HanSuk, Song SooChan, Lee KyungTae

College of Pharmacy, Kyung Hee University, Division of Life Sciences, Korea Institute of Science & Technology

KBP 93804A is a thermosensitive anti-tumor drug conjugate for local delivery of the drug to solid tumors. The platinum distribution of KBP 93804A 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.

[PE2-11] [10/19/2001 (Fri) 09:00 - 12:00 / Hall D]

Metabolic Difference of Omeprazole Hydorxylation in Korean Subjects in relation to the Genetic Polymorphism of CYP2C19

Jeong HyunCheol°, Lee YongBok

College of Pharmacy and Research Institute of Drug Development, Chonnam National University, Kwangju 500-757, Korea

Pharmacogenetic entities extensively studied and showing an interethnic difference in the drug-metabolizing enzyme activity include N-acetyltransferase (NAT2) and cytochrome P450 (CYP) 2C (CYP2C9 and 19) and CYP2D6. But, there were few investigations about CYP2C19 genotype in a Korean population. The aim of this study was to evaluate whether inter-individual differences in the pharmacokinetic disposition of omeprazole are attributed to the genetic polymorphism of CYP2C19, which occurred by CYP2C19m1 and CYP2C19m2 in a native Korean population. Sixty-seven healthy Korean volunteers were genotyped with respect to CYP2C19m1 and CYP2C19m2 alleles with polymerase chain reaction-based diagnostic tests. Of the 67 individuals analyzed, 13 were homozygous for the wild-type (wt) allele in both exon 5 and exon 4 (wt/wt, 19.4%, pattern G1), 27 were heterozygous for the CYP2C19m1 (wt/ml, 40.3%, G2), 7 were heterozygous for the CYP2C19m2 (wt/m2, 10.4%, G3), 15 were heterozygous for the two defects (m1/m2, 22.4%, G4), and 5 were homozygous for the CYP2C19m1 (m1/m1, 7.5%, G5). The allele frequencies of the m1 and m2 mutation were 0.39 and 0.16, respectively.

And then, the pharmacokinetic profile of omeprazole was examined in selected 15 volunteers (G1-G5, each three subjects). A correlation between the rate of metabolism of omeprazole and genotype was observed. There were significant ($p<0.05$ to 0.01) differences in the disposition kinetics of omeprazole between the subjects with patterns G1, G2, and G3 and the subjects with patterns G4 and G5. The results indicate that the 5-hydroxylation pathway of omeprazole is clearly impaired in subjects with m1/m2 and m1/m1.

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

The Effect of Bile juice on the Bioavailability and Pharmacokinetics of Acebutolol and Diacetolol After Oral Administration of Acebutolol

Choi JunShik°, Jung EunJung

College of Pharmacy, Chosun University

Acebutolol (ABT) is almost absorbed after oral administration, but its bioavailability is reduced because of considerable first-pass metabolism through the gastrointestinal and liver. The purpose of this study was to report the effect of bile juice on the bioavailability and pharmacokinetics of ABT and its metabolite, diacetolol (DAT) after oral administration of acebutolol in control rabbits and rabbits with bypass of bile duct. Plasma concentrations and the area under the plasma concentration-time curves (AUC) of ABT and DAT were increased compared to control rabbits, but that of DAT was significantly influenced ($p<0.05$). Absolute bioavailability(A.B.) of ABT in rabbits with bypass of bile duct(71.8%) was higher than control rabbits and also relative bioavailability(R.B.) of ABT was increased to 122%. Peak concentration time(Tmax) of ABT and DAT in rabbits with bypass of bile duct was significantly prolonged compared to control rabbits($p<0.01$). Mean Resident Time (MRT) of ABT and DAT in rabbits with bypass of bile duct were significantly increased ($p<0.05$) compared to control rabbits. Half-life of ABT and DAT in rabbits with bypass of bile duct were prolonged compared to control rabbits but that of DAT was significantly influenced ($p<0.05$). The results suggest that the dosage of acebutolol should be adjusted in disorder of bile juice flow.

[PE2-13] [10/19/2001 (Fri) 09:00 - 12:00 / Hall D]

Prediction of population pharmacokinetic parameters of aceclofenac using Monte Carlo simulations

Cho HeaYoung°, Yun JiHun, Lee YongBok

College of Pharmacy and Research Institute of Drug Development, Chonnam National University, Kwangju 500-757, Korea

The aceclofenac data analysis suggested that pharmacokinetic parameters were an important predictor of efficacy outcome. The purpose of this study is to estimate the relationship between individual pharmacokinetic and population pharmacokinetic parameters using Monte Carlo method. Plasma data from 21 healthy male subjects who participated in pharmacokinetic studies of aceclofenac were included in this analysis. After each subject received a single 100 mg oral dose of aceclofenac, 2-compartment model was fitted to the aceclofenac data using WinNonlin. In addition, one thousand Monte Carlo simulations were conducted assuming that the normal distribution of the pharmacokinetic parameters, such as A, B, α, β, Ka, K21 and Tlag, obtained from the individual subjects. The results demonstrate that Monte Carlo simulations as adjuncts to the current methods could be used for prediction of population pharmacokinetic parameters of aceclofenac.

[PE2-14] [10/19/2001 (Fri) 09:00 - 12:00 / Hall D]

Brain Distribution of Dehydroevodiamine in Rats