of intravenous azosemide in circulating blood for diuretic effects in NARs. The plasma protein binding of azosemide in control rats and NARs were 97.9 and 84.6%, respectively. The binding values of azosemide to rat α- and β-globulins were 82.6 and 68.9%, respectively, at α- and β-globulin concentrations equivalent to those in plasma of NARs. The percentage of intravenous dose of azosemide excreted in 8-h urine as unchanged diuretic was significantly greater in NARs (37.7 versus 21.0%) and this resulted in a significantly greater 8-h urine output in NARs (385 versus 221 mL/kg). In NARs, the AUC of azosemide was significantly smaller (505 versus 2790 mg min/mL). This could be due to significantly faster CLr (7.36 versus 0.772 mL/min/kg, because of significant increase in intrinsic renal active secretion) and CLnr (12.4 versus 3.05 mL/min/kg, because of approximately 3.5 folds increase in CYP1A2 in rats) than those in control rats. The renal sensitivities to azosemide were significantly greater in NARs than those in control rats in terms of 8-h urine output and 8-h urinary excretions of sodium, potassium,and chloride. This study supports the importance of binding of intravenous azosemide to α- and β-globulins in circulating blood for its diuretic effects.

[PE2-8] [10/19/2001 (Fri) 09:00 - 12:00 / Hall D]

HPLC Analysis, Stability, Blood Partition, and Protein Binding of an Antifibrotic Agent, Oltipraz

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A high-performance liquid chromatographic method was developed for the determination of Oltipraz in rat plasma and urine. The sample preparation was simple, 2 volumes of acetonitrile were added to deproteinize the biological sample. A 50-μl aliquot of the supernatant was injected onto a C_{18} reversed-phase column. The mobile phase, acetonitrile : 0.5 mM ammoniun acetate (55 : 45, v/v for rat plasma and 45 : 55, v/v for rat urine), was run at a flow-rate of 1.5 mL/min. The column effluent was monitored using an ultraviolet detector set at 305 nm. The retention times for Oltipraz in rat plasma and urine were approximately 5.8 and 8.6 min, respectively. The detection limits of Oltipraz in rat plasma and urine were 20 and 50 ng/mL, respectively. Oltipraz was relatively stable in various pH (1-12) solutions for up to 48-h incubation, however, it was unstable in pH 13 solution and rat plasma and urine. Oltipraz reached an equilibrium fast (within 30 s mixing manually) between plasma and blood cells of rabbit blood and the plasma-to-blood cells concentration ratios were independent of initial blood concentrations of Oltipraz, 1 and 5 μ
g/mL, the ratios ranged from 0.908 to 1.004. The binding of Oltipraz to 4% human serum albumin (HSA) was independent of Oltipraz concentrations ranging from 1 to 100 μg/mL using an equilibrium dialysis technique: the mean value was 95.0%. However, the binding of Oltipraz was dependent on HSA concentrations and the buffer pHs.

[PE2-9] [10/19/2001 (Fri) 09:00 - 12:00 / Hall D]

Pharmacokinetics and Pharmacodynamics of Intravenous Bumetanide in Mutant Nagase Analbuminemic Rats: Importance of Globulin Binding for the Pharmacodynamic Effects

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The importance of plasma protein binding of intravenous furosemide in circulating blood for its urinary excretion and hence its diuretic effects in mutant Nagase analbuminemic rats was reported. Based on the furosemide report, the diuretic effects of another loop diuretic, bumetanide, could be expected in analbuminemic rats if plasma protein binding of bumetanide is considerable in the rats. This was proved by this study. After intravenous administration of bumetanide, 10 mg/kg, to analbuminemic rats, the

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

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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 H2O2, 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

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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.