[PE2-5] [04/21/2000 (Fri) 10:30 - 11:30 / [1st Fl, Bldg 3]]

In vitro metabolism of YH1885 by human liver microsomes and recombinant human cytochrome P450s

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YH1885,[5,6-dimethyl-2-(4-fluorophenylamino)-4-(1-methyl-1,2,3,4-tetrahydroisoquinolin-2-yl) pyrimidine hydrochloride], is a novel acid pump antagonist being developed by Yuhan Research Center as an antiulcer agent. To evaluate the metabolic profile and identify cytochrome P450(CYP) isoforms involved in the metabolism of YH1885 in human, we investigated the hepatic metabolism of YH1885 by using human liver microsomes and recombinant human cytochrome P450s. We also investigated the interaction of YH1885 with specific markers of CYP isoforms.
The formation of metabolites was characterized by KM and Vmax. The high KM values of major metabolites (≥ 219μM) suggested relatively low affinity of YH1885 to cytochrome P450. Therefore, YH1885 is likely to be hardly metabolized in human liver. The formation of major metabolites was mainly mediated by CYP3A4 and CYP1A2. The Ki values for caffeine 3-demethylation (CYP1A2) and testosterone 6β-hydroxyation (3A4) were much higher than the presumed concentration of YH1885 in clinical studies. Therefore, it is expected that YH1885 would cause little interaction with other drugs.
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[PE2-6] [04/21/2000 (Fri) 10:30 - 11:30 / [1st Fl, Bldg 3]]

Pharmacokinetics of BR-A657 in rats ; A New angiotensin II receptor antagonist

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BR-A657 is analogue of losartan potassium which is orally active non-peptide A II receptor antagonist. In this study BR-A657 was determined by high-performance liquid chromatography in rat plasma with ultraviolet detection and its pharmacokinetic parameter in i.v. administration was calculated. Plasma samples were extracted by methyl tert.-butyl ether in pH 3 then back-extracted by 0.05 M NaOH Samples were analyzed by reversed-phase HPLC system using μBondapak C18 column with ultraviolet detection at 261 nm. Detection limit was 20nM. 50 mg/kg of potassium salt and base form of BR-A657 was orally administered to rats. Both form of BR-A657 were rapidly absorbed and Cmax was 20 minutes. But bioavailability of potassium salt form was better than that of base form. In 1 mg/kg intravenous administration to rats, plasma concentration-time profile was best characterized by 2-compartment model. T1/2α and T1/2β were 0.02±0.01 hr, 0.24±0.10 respectively. Clearance, volume of distribution, and AUC were 5.75±1.18 L/kg/hr, 0.37L/kg/hr, 179.03±37.74 ng·hr/ml, respectively

[PE2-7] [04/21/2000 (Fri) 10:30 - 11:30 / [1st Fl, Bldg 3]]

Pharmacokinetic study of CWJ-a-5

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Pharmacokinetics of 1-(4-methylpiperazinyl)-3-phenylisoquinoline hydrochloride (CWJ-a-5), a novel antitumor 3-arylisoquinoline derivative, was studied after intravenous (iv), oral (po) and hepatoportal (pv) administration in rats. A simple high-performance liquid chromatographic method was developed to determine the concentrations of CWJ-a-5 in plasma, bile and urine. A linear pharmacokinetic behavior was observed after iv administration of up to 20 mg/kg of CWJ-a-5. The half-life of CWJ-a-5 in the post-distributive phase (t1/2β), total-body plasma clearance (CLt), and volume of distribution (Vdss) were 86.91 min, 5.72 L/hr/kg and 9.79 L/kg, respectively, after iv administration of 10mg/kg. Biliary and urinary excretion of CWJ-a-5 was less than 1% after iv injection of 10mg/kg. The bioavailability of CWJ-a-5 after po and pv administration (50mg/kg and 10mg/kg, respectively) was 64.3% and 72.2%, respectively. Gastrointestinal bioavailability was calculated to be 73.3%. The partition coefficient of CWJ-a-5 between n-octanol and water was 1.25 (log P=0.10). Plasma protein binding of CWJ-a-5 measured by the ultrafiltration method was greater than 95%.

[PE2-8] [04/21/2000 (Fri) 10:30 - 11:30 / [1st Fl, Bldg 3]]

Pharmacokinetic Disposition of Polyethylene Glycol-Modified Salmon Calcitonins in Rats

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This study reports the pharmacokinetic disposition of polyethylene glycol (PEG)-modified salmon calcitonin (sCT) based on the number of attached PEG molecules. PEG-modified sCT was prepared by covalent linkage with succinimidyl carbonate monomethoxy polyethylene glycol. Mono- and di-PEG-sCTs were separated by size exclusion and reverse phase HPLC, and were radioiodinated by the chloramine-T method with Na125I. 125I-mono-PEG sCT, 125I-di-PEG-sCT and unmodified 125I-sCT were administered to rats by i.v. injection. Serial blood samples, urine and various tissue samples were taken for the determination of radioactivity. Di-PEG-sCT exhibited a significantly reduced systemic clearance (2.3 vs. 11.9 ml/min/kg) and steady-state volume of distribution (229.9 vs. 603.1 ml/kg), while mono-PEG-sCT showed a prolonged elimination half life (189.1 min vs. 59.8 min) over unmodified sCT. The extent of urinary excretion of the PEG-modified sCTs was higher than for the unmodified sCT but all these chemicals were excreted in urine in small quantities (<0.6%). There was a tendency of reduced accumulation of PEGylated sCTs in tissues, with its reduction being inversely proportional to the molecular size. Accumulation of the total radioactivity of the unmodified and PEG-modified sCTs was highest in the liver followed by kidneys, lungs, spleen, heart and thyroid. When expressed per tissue gram weight, however, the highest radioactivity was found in the kidneys. PEGylated sCTs may have greater therapeutic potential via reduced systemic clearance and prolonged elimination half-life over unmodified sCT

[PE2-9] [04/21/2000 (Fri) 10:30 - 11:30 / [1st Fl, Bldg 3]]

Comparison of iron distribution between 59Fe alone and 59Fe-difructose complexes in the rat

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The purpose of this study was to determination the disposition characteristics of iron with difructose (di-D-fructosefuranose dianhydries, DFAs) in rats. We have prepared the iron-DFA III.complex at molar ratio 1:1 and iron-DFA IVcomplex at molar ratio 1:1. To determination of iron distribution, we performed the whole-body autoradiography (WBA) and measured the intensities of ^{59}Fe in whole blood after oral administration of ^{59}Fe alone and ^{59}Fe-DFA complexes at 100uCi/kg. The relative