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