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

intensities represented by [photo-stimulated luminescence (PSL)-background (BG)/area (S)]values in WBA. The intensities of ^{59}Fe in case of iron-DFA complexes were higher than that of iron alone in almost organ, liver, spleen, heart and kidney and so on. The concentration-time profiles of iron in whole blood were showed that the iron concentration after administration of iron-DFA complexes was greater than that of iron alone. These results suggest that the DFA III and IV may be used as a promoter of iron absorption for the treatment of iron deficiency anemia.

[PE3-1] [04/21/2000 (Fri) 10:30 - 11:30 / [1st Fl, Bldg 3]]

PREPARATION AND CHARACTERIZATION OF POLYLACTIC ACID NANOPARTICLES WITH POLYETHYLENE IMINE AS DNA CARRIER

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Using the cationic lipid and polycations the non-viral gene delivery has been developed for gene transfer. The size, charge and solubility of the complex formed by DNA and polycation are dependent on the charge ratio of the polycations and DNA. In the present study, we report the preparation and characterizations of the polylatic acid (PLA) and polylactide-co-glycolide (PLGA) nanoparticles containing PME185/?gal, a mammalian expression constract that expresses ?galactosidase as a model DNA. The effect of polyethylene imine (PEI) on the characteristics of nanoparticles and adsorption efficiency with DNA were also examined. Nanoparticles were prepared by a dialyzing method. The shape and morphology of nanoparticles were characterized by scanning electron and transmission electron microphotograph. The stability of the nanoparticles in suspension was evaluated by turbidity measurement. Complex formation between the nanoparticles and plasmid DNA was examined by gel electrophoresis. When the PEI amount in polymers was increased, the mean diameter of the resulting nanoparticles was decreased. The ?potential of nanoparticles showed a highly negative value in PLA or PLGA nanoparticles without PEI, while a positive value in the PLA or PLGA nanoparticles with PEI. The nanoparticles in suspension exhibited good dispersion stability until 15 days of incubation though a small decrease in turbidity at the initial time. An increase in nanoparticle amount caused a gradual disappearance of the DNA. This indicates that all of DNA was trapped on the surface of the nanoparticles.
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[PF1-1] [04/21/2000 (Fri) 10:30 - 11:30 / [1st Fl, Bldg 3]]

Preliminary Study on Architecture of Laboratory Information Management System for Clinical Trial

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Clinical trial is one of keystones for the development of new drugs and needs total management of huge amount of data acquired from many different sources and statistical analysis of the acquired data. The management of clinical data from clinical trial should be compliant with several regulations such as GCP, GLP and GALP. Computerized system for experimental design of the clinical study and collection, manipulation, statistical treatment, reporting and evaluation of clinical data is needed to be compliant to those regulations. This system should be under a certain level of security on data management, user authentication, audit trailing. An architecture of laboratory information management system is proposed on the Internet environment with PC server. The proposed system includes Linux as OS, Oracle as DBMS, Apache as web server and gcc, Perl, PHP as development tools. The system is designed to have 5 modules: Administrator module, Clinical trial design module, Data entry module, Data management module, Data retrieval/Reporting module. The proposed model is designed to be compliant to the related regulations and a set of security measures are proposed for the system.