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MECHANISM OF ABNORMAL LIVER UPTAKE OF Tc-99m-DIPHOSPHONATES (Tc-99m-DIPs). M. Hayashi, K. Takahashi and M. Hazue. Research and Development, Technical Department, NIHON MEDI-PHYSICS CO., LTD., Takarazuka.

Some investigators reported that liver uptake of Tc-99m-DIPs increased proportional to Al^{3+} concentration in plasma and in Tc-99m-DIPs solution.

In our studies to develop Tc-99m-hydroxymethylene diphosphonate (Tc-99m-HMDP) as a new bone scanning reagent, it was revealed that higher concentration of HMDP in Tc-99m-HMDP solution caused higher liver uptake even if Al^{3+} levels were lowered satisfactorily.

In experiments in vitro, it was found that Tc-99m-HMDP solution became turbid at the elevated concentration of HMDP under physiological concentration of Ca^{2+} ions. The change of turbidity indicated the colloid formation and coincided with the change of liver uptake. Furthermore, we found that the HMDP- Ca^{2+} colloid could pass through 0.2 μ filter.

On these investigations, we concluded that the accumulation of radioactivity in liver was the result of HMDP- Ca^{2+} colloid formation in vivo.

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Tc-99m(Sn)-N-PYRIDOXYLAMINATES: A NEW SERIES OF HEPATOBILIARY IMAGING AGENTS I. SYNTHESIS OF LIGANDS AND PREPARATION OF Tc-99m COMPLEXES. M. Kato-Azuma and M. Hazue Research & Development, Technical Department, NIHON MEDI-PHYSICS CO., LTD., Takarazuka.

A new approach to Tc-99m labeled hepatobiliary imaging agents was developed to overcome some disadvantages associated with the Tc-99m(Sn)pyridoxylideneamine system: catalytic hydrogenation of the imine moiety of a pyridoxylideneamine gave stable, isolatable N-pyridoxylamine, and this new ligand was then complexed with Tc-99m by the stannous reducing method (patent pending).

Three derivatives of N-pyridoxylamine were currently synthesized via the method reported by Heyl et al. using Pt or Pd catalyst: they were N-pyridoxyl-L-phenylalanine, -L-tryptophan and -DL-5-methyltryptophan. After an intensive study on the Tc-99m labeling conditions, stable Tc-99m complexes were obtained, and each of them showed sharp, single peak on thin layer chromatogram. The TLC system was designed so as to discriminate the Tc-99m complex from Tc-99m pertechnetate and/or reduced, hydrolyzed Tc-99m species: the labeling efficiency for each complex was found to be practically 100 % for more than 48 hr after the labeling.

The in vivo distribution of each Tc-99m complex in rats after i.v. administration was quite identical to that of the corresponding pyridoxylideneamine derivative, and the 5-methyltryptophan derivative showed superior in vivo behavior as a new hepatobiliary imaging agent.

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Tc-99m(Sn)-N-PYRIDOXYLAMINATES: A NEW SERIES OF HEPATOBILIARY IMAGING AGENTS II. PREPARATION OF DL-5-METHYLTRYPTOPHAN DERIVATIVE AND EVALUATION OF ITS IN VIVO DISTRIBUTION IN ANIMALS. M. Kato-Azuma and M. Hazue Research & Development, Technical Department, NIHON MEDI-PHYSICS CO., LTD., Takarazuka.

An intensive study was performed on Tc-99m(Sn)-N-pyridoxyl-DL-5-methyltryptophan [Tc-99m(Sn)PHMT], a new candidate for a superior hepatobiliary imaging agent.

Various factors for the preparation of the Tc-99m complex were examined, and conditions for the stabilization of the complex were also investigated. These studies enabled us to produce this agent in its Tc-99m labeled, i.e., ready-to-injection form.

The dynamic in vivo behavior of Tc-99m(Sn)PHMT was firstly evaluated in rats via i.v. administration. The blood clearance and hepatic uptake of this agent were quite fast, and the rate was almost comparable to that of colloid-type liver imaging agents. The hepatobiliary transport was also very rapid: 92 % of the total injected dose has arrived in the small intestine through the liver during the first hour. The renal excretion into urine was only 2 % for the first hour.

The sequential scintiphotos of a rabbit after i.v. administration of Tc-99m(Sn)PHMT showed an identical dynamics of radioactivity to that observed in rats. The in vivo dynamics of this agent in rabbits was also compared with that of Tc-99m(Sn)EHIDA.

The toxicity studies on PHMT and final injectable solution revealed a wide margin of safety for the proposed human dose.

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Tc-99m(Sn)-N-PYRIDOXYLAMINATES: A NEW SERIES OF HEPATOBILIARY IMAGING AGENTS III. EFFECT OF BSP INTERVENTION ON BILIARY EXCRETION OF DL-5-METHYLTRYPTOPHAN DERIVATIVE. M. Kato-Azuma and M. Hazue Research & Development, Technical Department, NIHON MEDI-PHYSICS CO., LTD., Takarazuka.

It has been reported that the degree of competition of Tc-99m labeled hepatobiliary imaging agents with serum bilirubin can be estimated through the BSP intervention study since BSP shares same biliary excretion pathway with bilirubin. We tried the BSP intervention study on Tc-99m(Sn)PHMT (see, preceding two abstracts), and the results were compared with that obtained for Tc-99m(Sn)-EHIDA and Tc-99m(Sn)PI.

A rat was continuously infused through the femur vein with BSP solution at a rate of 2.5 μ mole BSP/min/Kg body weight over a period of 45 min, which initiated at 15 min before the injection of Tc-99m species. This dose of BSP corresponds twice the transport maximum in rat. After the bolus i.v. administration of Tc-99m species, each of the 3 min bile flow was sequentially collected over 90 min period through a cannula inserted into the common bile duct. The successive radioactivity measurement of each bile fraction gave differential or cumulative biliary excretion curve for each of the Tc-99m agents.

The results of our current study revealed that Tc-99m(Sn)PHMT was much less affected by BSP compared with Tc-99m(Sn)-EHIDA or -PI. These findings suggest the possibility of successful hepatobiliary imaging with Tc-99m(Sn)PHMT under the elevated serum bilirubin.