C. Radiopharmaceuticals and Radionuclides

70

Tc-99m LABELING OF PROTEINS USING BIFUNCTIONAL AGENT (II): Tc-99m LABELED HSA.

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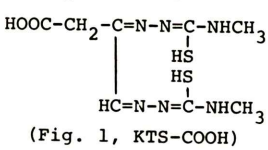
A new bifunctional chelating agent, 3-oxobutyral-bis(N-methylthiosemicarbazone)-carboxylic acid, (KTS-COOH)(Fig. 1), is synthesized. Labeling of HSA with Tc-99m using this agent is carried out by the following method: (a) KTS-COOH is first prepared by a mixed anhydride method, and then labeled with Tc-99m. (b) KTS-COOH is labeled with Tc-99m and then conjugated with HSA in the presence of carbodiimide. In both cases, Tc-99m is efficiently labeled by using tin adsorbed resin; Tc-99m labeled HSA-conjugate is purified through Sephadex column chromatography (G-25). In vitro stability, on standing (24hr), is very high, and no free Tc-99m is detected. In vivo studies show a significantly good blood level, almost comparable to the data reported with I-131-HSA, and better than the available commercial kit of Tc-99m-HSA. Further studies on this agent are now under way.



(Fig. 1, KTS-COOH)

71

EFFECT OF METALS AND OXIDANTS IN Tc-99m LABELED COMPOUNDS ON BIODISTRIBUTION IN RATS AND LABELING EFFICIENCY.

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Metals and oxidants in Tc-99m pertechnetate have been reported to have a detrimental effect on biodistribution and labeling efficiency of various Tc-99m labeled compounds. The mechanism of the effect, however, is not clear yet. The purpose of the present study is to investigate the effect of metals(Al,Mo) and oxidants(H_2O_2,NaOCl,O_2) in Tc-99m pertechnetate solution on the biodistribution in rats and labeling efficiency for Tc-99m labeled compounds. The labeled compounds were prepared with four diagnostic kits of our product line, i.e. Sn-colloid, DMSA, EHDP and PI. The presence of Mo(1μg/ml) in Tc-99m DMSA resulted in a increase of liver uptake while the uptake of the objective organ, the kidneys, decreased. The liver uptake of Tc-99m(Sn)colloid also decreased with the same concentration. The presence of H_2O_2(5μg/ml) or O_2(air bubbling for 5 min : 15 cc/min) as oxidants in Tc-99m (Sn)colloid showed a gradual increase of lung uptake with time after labeling, but free Tc-99m pertechnetate was not detected.

72

IN VIVO LABELING OF RED BLOOD CELLS WITH Tc-99m USING STANNOUS PYRIDOXYLIDENEAMINATES.

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The procedure of in vivo labeling of red blood cells (RBCs) with Tc-99m has been attracting much interest because of the simplicity of the procedure, the high labeling efficiency and its superior in vivo stability. We have currently evaluated several stannous pyridoxylideneaminates as the stannous ion sources for in vivo RBC labeling with Tc-99m, while the i.v.injection of stannous pyrophosphate followed by pertechnetate is a widely accepted procedure.

In spite of a considerable variety of stannous preparations, rapid and efficient RBC labeling was obtained with each stannous chelate, and the results were equal or superior to that obtained with stannous phosphates. These results suggest that the role of the ligands is merely to stabilize the divalent state of the tin. The optimal procedures were evaluated using stannous pyridoxylideneisoleucine (Sn-PI). The maximum in vivo RBC labeling was obtained with; 1) intravenous injection of 10-20 μg/Kg body weight of Sn(II) as Sn-PI, 2) waiting for 15-30 min to ensure saturation of RBCs with Sn(II) and 3) an intravenous injection of the appropriate activity of Tc-99m as pertechnetate. These procedures were effective in rats and rabbits, and the blood pool visualization was stable for more than 1 hr after the TcO_4^- injection. Further studies will be performed in higher animal species.

74

DIFFERENT MOLECULAR CONFORMATION OF Tc-99m PYRIDOXILIDENEAMINOACIDS AND ITS EFFECT ON BILIARY EXCRETION.

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Tc coordinated in mono, di or polynuclear state with penicillamine (PEN) showed different pharmacodynamic distribution. Tc-99m-Pyridoxilideneglutamate (PG) prepared by Sn-resin kit and Tc-99m-pyridoxilideneisoleucine (PI) of Kato's are comparatively tested by IN VITRO (thin layer and sephadex column chromatography (G-15), exchange reaction with PEN, octanol extraction) and IN VIVO studies (mice biodistribution, metabolic studies, protein binding, rat bile excretion). PG similar to Baker's complex is of high molecular weight and low lipophilicity (octanol extraction 42%, cumulative bile excretion 41%, 1hr) but of great stability. No ligand exchange, no metabolic change of the injected compound and 40% excreted in faeces (24hr). PI, on the other hand, is a highly lipophilic (octanol extraction 93%, cumulative bile excretion 76.7%, 1hr) of lower molecular weight and stability which undergoes exchange reaction, forming a mononuclear complex of PEN. So, a mononuclear complex with Tc(IV) bis coordinated with ligand is postulated. PG reaches its stability through Tc in dinuclear state bis coordinated with the ligand. Larger amount of PI bound to protein (52% versus 33%) but metabolic changes are detected in bile, urine and 27.4% are excreted in faeces (24hr).