

A ^{99m}Tc -LABELED REPLACEMENT FOR ^{131}I -ROSE BENGAL IN LIVER AND BILIARY TRACT STUDIES

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A ^{99m}Tc -labeled replacement for ^{131}I -rose bengal in liver and biliary tract studies has been developed. This agent, ^{99m}Tc -labeled Hepato-Biliary ScintigraphinTM, is rapidly cleared from the plasma by the liver with close to 100% hepatic extraction efficiency, followed by nearly complete excretion of activity in bile. Its utility for studying liver, gallbladder, and biliary tract morphology and function are demonstrated.

Although ^{99m}Tc -labeled colloids are used routinely for the evaluation of regional hepatic blood flow and reticuloendothelial activity, it would be useful to have a ^{99m}Tc -labeled agent which would be secreted by the liver into the bile allowing for assessment of biliary as well as hepatic excretory function. We have developed such an agent.

MATERIALS AND METHODS

Equal parts of 3 mM mercapto-iso-butyric acid and 1 mM SnCl_2 are used. When one part of $^{99m}\text{TcO}_4^-$ is added to one part of this mixture, labeling is rapid and binding of ^{99m}Tc is essentially complete. Daily intravenous administration to dogs of 1.0–1.5 ml/kg body weight of the mixture for 14 consecutive days failed to result in significant changes in peripheral blood elements and serum parameters measured by a series of SMA No. 12 panels. Histologic examination of dogs sacrificed immediately after such daily administrations as well as histologic examination of rats sacrificed immediately after receiving 1.8 ml/kg of the mixture for 14 consecutive days failed to show any tissue changes related to administration of the agent.

RESULTS

Following intravenous administration of ^{99m}Tc -MPI-Hepato-Biliary ScintigraphinTM (^{99m}Tc -HBS) to dogs and rodents, activity distributes in the plasma

from where it is cleared with an initial $t_{1/2}$ of less than 2 min. This initial clearance rate is comparable to that obtained with intravenously administered radiocolloids in these species. In the dog the slope of the plasma disappearance curve diminishes after 5 min, becoming fairly flat at 30 min with approximately 5% of the administered dose present in the plasma at that time (Fig. 1). Plasma was removed

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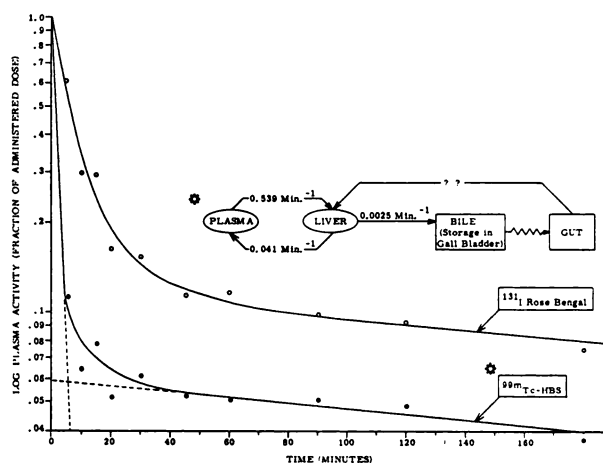


FIG. 1. Plasma clearance of ^{99m}Tc -Hepato-Biliary ScintigraphinTM and ^{131}I -rose bengal administered simultaneously i.v. to a dog (^{131}I -rose bengal obtained from commercial source and not analyzed for free ^{131}I). Kinetic model shown is described in text and values of rate constants were calculated from plasma clearance data for ^{99m}Tc -HBS shown in figure. For this dog, under nembutal anesthesia, fractional rate of hepatic feedback of ^{99m}Tc -HBS into plasma is about 7.6% of fractional rate of clearance from plasma by liver. Mean bile turnover rate is 0.25%/min.

from rats 5, 15, and 30 min after intravenous administration of ^{99m}Tc -HBS, and the plasma, containing residual activity, was reinjected into other rats. The in vivo distribution of activity in rats receiving plasma of rats previously given ^{99m}Tc -HBS was similar to that noted in the rats receiving the ^{99m}Tc -HBS directly. Thus, the apparent slow plasma clearance of activity following the initial rapid phase of clearance is probably due to feedback of ^{99m}Tc -HBS into the plasma from extravascular sites rather than re-appearance of ^{99m}Tc activity in plasma as $^{99m}\text{TcO}_4^-$. These data also suggest that the ^{99m}Tc activity in the plasma is bound to a single HBS species rather than existing as several ^{99m}Tc -HBS forms having varying plasma clearance kinetics.

The change in tissue ^{99m}Tc activity with time following i.v. administration of the ^{99m}Tc -HBS to rats is shown in Fig. 2. All numbers are presented as activity in the tissue in the given organ expressed as percent of activity remaining in the body at the indicated time. This figure does not account for activity excreted in urine or feces at the time of sacrifice. It can be seen that as early as 5 min after administration of ^{99m}Tc -HBS to the rat, approximately 78% of the remaining activity is in the liver and 6% in the gut. The liver activity is progressively cleared with concomitant increase in gut activity such that 3 hr after i.v. administration of ^{99m}Tc -HBS, approximately 4% of the remaining activity remains in the liver and 92% is found in the gut.

In a series of seven rats sacrificed 1 hr after i.v. administration of ^{99m}Tc -HBS, the following tissue distribution of activity was noted (expressed as percent of administered dose): liver $34.8 \pm 10.0\%$, gut $50.8 \pm 11.2\%$, urine and bladder $3.6 \pm 0.9\%$, and kidneys (2) $1.9 \pm 0.8\%$. Since no evidence of

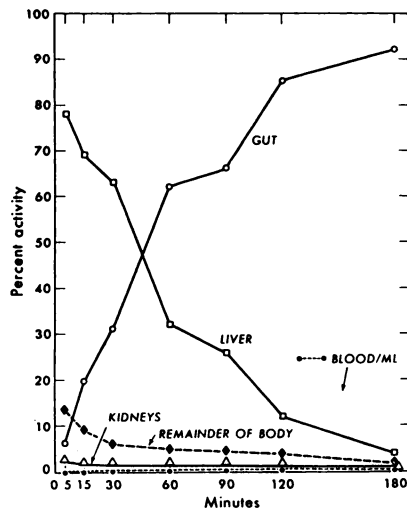


FIG. 2. Tissue distribution of activity following i.v. administration of ^{99m}Tc -Hepato-Biliary ScintigraphinTM in rats. (Each point represents tissue samples of two rats. All data are expressed as percent of activity remaining in body at time of assay.)

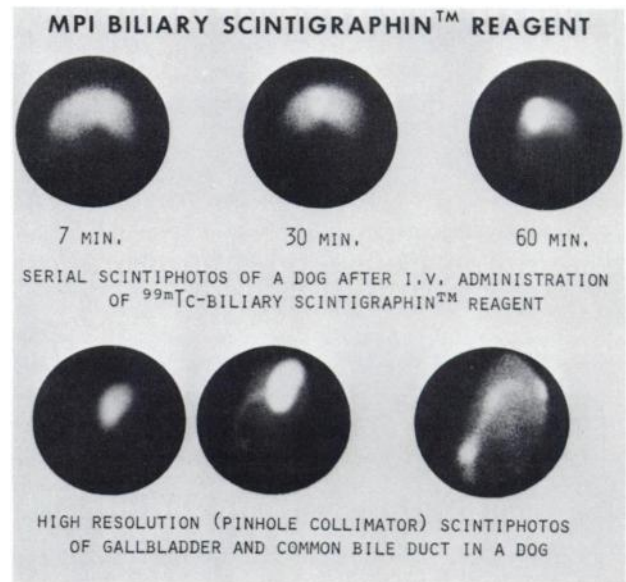


FIG. 3. In vivo scintigraphy of ^{99m}Tc -MPI Hepato-Biliary ScintigraphinTM. Upper scintiphotos were obtained using 4,000 parallel-hole collimator, and lower scintiphotos were obtained using pinhole collimator fitted to scintillation camera. Liver is well visualized within 7 min after administration, similar to that seen with ^{99m}Tc colloids except for absence of activity in spleen with ^{99m}Tc -HBS. At 30 min, concentration of activity in gallbladder is clearly noted with such activity becoming prominent at 60 min. By suitable adjustment of image intensity gallbladder (lower left), gallbladder and common bile duct (lower center), and common bile duct alone (lower right) can be imaged with high resolution.

free pertechnetate was noted either in vitro or in vivo with ^{99m}Tc -HBS, a reasonable approximation of the ^{99m}Tc -HBS activity cleared from the plasma by the liver may be taken as the sum of liver and gut activity (i.e., from biliary excretion) at any given time. Twenty-four hr after i.v. administration of ^{99m}Tc -HBS to rats, approximately 93% of administered activity was found to have been excreted from the body.

In a dog sacrificed 2 hr after i.v. administration of ^{99m}Tc -HBS, the following distribution of activity expressed as percent of administered dose was obtained: liver 47.6%, gallbladder (plus contents) 28.4%, gut 11.0% (total of approximately 87% cleared from plasma by liver), and kidneys (2) 0.4%. Approximately 7% of administered activity was excreted in urine at this time. Since, from Fig. 1, at 2 hr approximately 5% of the administered activity remains in the plasma, a very small fraction of administered activity remains distributed among all other organs.

These data are consistent with the ^{99m}Tc -HBS kinetics model shown in Fig. 1 which identifies plasma as the initial distribution space for a single labeled species where it is cleared by the liver with a plasma extraction efficiency of approximately 100% (e.g., comparable to most colloids). Once in the liver the ^{99m}Tc -HBS is either excreted in the bile

or released back into the plasma where it continues to engage in a liver-plasma feedback system. The ^{99m}Tc -HBS excreted in the bile enters the gut and is excreted in the feces. No appreciable oxidation of the ^{99m}Tc to pertechnetate occurs in vivo and any enterohepatic recirculation of the ^{99m}Tc -HBS would not be expected to contribute to systemic plasma ^{99m}Tc -HBS levels because of the high extraction efficiency of the liver for this material.

Figure 3 shows in vivo scintigraphy of a dog following i.v. administration of ^{99m}Tc -HBS. All scintiphotos were obtained using a standard pinhole collimator fitted to a Searle Radiographics HP scintillation camera. Seven minutes after i.v. administration of ^{99m}Tc -HBS, hepatic scintigraphy is comparable to that obtained using ^{99m}Tc -colloids except for absence of activity in the spleen. At 30 min the gallbladder is visualized and at 60 min the gallbladder activity is predominant. The lower scintiphotos taken 60–120 min after administration show good resolution of activity in the gallbladder taken at an appropriate intensity for gallbladder visualization (left) and appearance of activity in the common bile duct (center) and region of the ampulla (right) in high-

intensity scintiphotos intended to accentuate the small activity present in the common bile duct.

DISCUSSION

A simple kit for production of a ^{99m}Tc -labeled Hepato-Biliary ScintigraphinTM (^{99m}Tc -HBS) agent has been developed. Initial rapid clearance of ^{99m}Tc -HBS from plasma by liver suggests close to 100% hepatic extraction efficiency. Hepatic ^{99m}Tc -HBS is excreted into the bile and engages in a liver-plasma feedback system, the net effect of which is a rapid, near quantitative excretion of activity in bile. Scintigraphic evaluation of activity shortly after i.v. administration of ^{99m}Tc -HBS yields images comparable to those obtained with ^{99m}Tc -colloids except for absence of activity in the spleen. Subsequent serial scintiphotos provide a measure of regional capacity of liver to excrete ^{99m}Tc -HBS in bile and allows for high-resolution scintigraphic imaging of gallbladder and biliary tract morphology and function.

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