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[54] **HEPATO-BILIARY RADIOPHARMACEUTICAL COMPRISING 2-MERCAPTOISOBUTYRIC ACID CHELATING REDUCED TECHNETIUM-99M**

[75] Inventors: **Harry S. Winchell,** Lafayette; **Archie S. Khentigan,** San Francisco; **Hong Lin,** Berkeley, all of Calif.

[73] Assignee: **Medi-Physics, Inc.,** Emeryville, Calif.

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[52] **U.S. Cl.**..... **424/1;** 250/303; 260/429 R; 260/429.7

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[58] **Field of Search**..... 424/1; 260/429.7, 429 J, 260/429 K, 429 R; 250/303, 363

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Primary Examiner—Benjamin R. Padgett
Assistant Examiner—C. Nucker
Attorney, Agent, or Firm—Samuel L. Welt; Jon S. Saxe; R. Hain Swope

[57] **ABSTRACT**

A radiopharmaceutical comprising 2-mercaptoisobutyric acid chelating reduced technetium-99m for scintigraphically imaging the liver and biliary tract morphology and function and to a method for instantly making the radiopharmaceutical.

7 Claims, No Drawings

HEPATO-BILIARY RADIOPHARMACEUTICAL COMPRISING 2-MERCAPTOISOBUTYRIC ACID CHELATING REDUCED TECHNETIUM-99M

BACKGROUND OF THE INVENTION

Heretofore, various dyes have been labeled with iodine radioisotopes for combined imaging of the liver and biliary tract. An imaging agent such as iodine-131 labeled rose bengal has proven useful; however, the relatively high radiation dose associated with it has limited the extent of its use. The *Journal of Nuclear Medicine*, August, 1972, Vol. 13 No. 8, at pages 652–4, suggests use of technetium-99m labeled D-penicillamine as a cholescintigraphic agent prepared in acid solution, heated and then neutralized before use. The *Journal of Nuclear Medicine*, June 1973, Vol. 14 No. 6 at pages 411–12, suggests several technetium-mercaptide derivatives as liver specific imaging agents. These technetium labeled agents would result in diminished absorbed radiation doses.

SPECIFICATION

This invention relates generally to such hepato-biliary imaging radiopharmaceuticals and more particularly to a new liver specific radiopharmaceutical useful for studying liver, gall bladder and biliary tract morphology and function.

The pharmaceutical consists of an aqueous solution of 2-mercaptoisobutyric acid chelating reduced 99m-technetium. A preferred form utilizes stannous tin as a reducing agent for the technetium-99m. In this form the imaging agent is simply and rapidly prepared by mixing a reagent containing the 2-mercaptoisobutyric acid and stannous tin with oxidant-free technetium-99m pertechnetate which is readily available in physiological saline solution.

In vivo distribution studies of the labeled material in experimental animals after intravenous injection show initial rapid clearance of the radioactivity from the blood plasma specifically by the liver with subsequent, almost complete, excretion into the biliary tract.

The principal object of this invention is to produce a technetium-99m radiopharmaceutical which rapidly accumulates in the liver and then is excreted from the liver to the biliary tract so as to be useful for hepatic-biliary morphology and function studies.

Another object of this invention is to produce such a radiopharmaceutical in a simple and rapid labeling procedure which does not involve heating or complicated pH adjustment.

Other objects and advantages of the new pharmaceutical and method will become apparent upon consideration of the following description of a specific example.

The radiopharmaceutical has been prepared from a reagent made by mixing equal parts by volume of an aqueous solution of 3m$\bar{M}$ 2-mercaptoisobutyric acid and 1m$\bar{M}$ stannous chloride. To one part by volume of reagent is added one part of oxidant-free 99m-technetium pertechnetate in physiological saline solution. The combined solutions are mixed thoroughly by shaking. The technetium labeling is rapid. The binding of 99m-technetium is essentially complete immediately after mixing and the agent is immediately ready for intravenous administration. The radiopharmaceutical should be used within two hours after preparation.

Other proportions of 2-mercaptoisobutyric acid and stannous chloride can be used. No significant difference in in vivo distribution has been noted if the labeled pharmaceutical is prepared from reagent made with 1 m$\bar{M}$ stannous chloride mixed with an equal volume of 3, 5, 7.5 or 10 m$\bar{M}$ concentrations of 2-mercaptoisobutyric acid. Similarly, no significant difference in the in vivo distribution was observed for the radiopharmaceutical wherein the reagent was prepared with equal volumes of 1 m$\bar{M}$ stannous chloride and various 3 m$\bar{M}$ solutions of 2-mercaptoisobutyric acid adjusted in pH through the range of 2.9 to 7. The pH of 3 m$\bar{M}$ 2-mercaptoisobutyric acid is about 2.9 and the pH range of the reagent of the specific example above is 2.5 to 3.5. Varying concentrations of stannous chloride or varying proportions of reagent to technetium-99m pertechnetate also do not significantly affect in vivo distribution.

Following intravenous administration of the pharmaceutical in experimental animals, the activity distributes in the blood plasma from which it is cleared by the liver exponentially, with a half-time of less than two minutes. The initial clearance rate is comparable to that obtained with intravenously administered radiocolloids in the same animal species and extraction efficiency of the liver is almost 100%. The slope of the disappearance curve for radioactivity in the blood plasma diminishes after five minutes, becoming fairly flat at 30 minutes with approximately five percent of the administered dose remaining in the blood plasma at that time. There is negligible uptake in the kidneys and spleen.

For example, in experimental rats, as early as five minutes after administration over 75% of the remaining activity was in the liver and 6% in the gut. The liver activity progressively cleared through the biliary tract to the gut. Three hours after administration, approximately 4% of the remaining activity was in the liver and 91% was found in the gut. Activity in the kidneys and spleen of animals sacrificed one hour after administration was negligible. Approximately 93% of the administered activity was found to have been excreted from the body within 24 hours after its administration.

The radiopharmaceutical is particularly useful for liver-biliary tract function studies. In scintiphotographs taken of experimental dogs following intravenous administration using a standard pinhole collimator fitted to a Nuclear Chicago H-P scintillation camera, the liver was clearly visualized seven minutes after administration comparable to that obtained using 99m-technetium labeled colloids, except that there was no activity seen in the spleen. At thirty minutes, the gall bladder was visualized and at 60 minutes after administration the gall bladder activity was predominant. Scintiphotographs taken 90 to 120 minutes after administration showed with good resolution the activity in the common bile duct and in the region of the ampula.

The foregoing example and distribution data are illustrative of the improved pharmaceutical and the simple method for instantly making it. Reducing agents for technetium-99m other than stannous tin may be used to make the described pharmaceutical, i.e., ferrous, titanous, zirconyl and chromous ions as well as 2-mercaptoisobutyric acid itself in high concentration or low pH or elevated temperature as is known in the art. An hepato-biliary scintographic agent has been formed by (a) heating technetium-99m pertechnetate in the presence of 2-mercaptoisobutyric acid (MIBA) for 15 minutes at 100°C or (b) by contacting technetium-99m pertechnetate with high concentrations of

2-mercaptoisobutyric acid (MIBA), e.g. greater than 10 millimolar, for several hours.

In view of the fact that various radiopharmaceuticals which do not accumulate generally in normal tissue other than the target organ being studied, have been found to localize in infarcts and tumors, the described radiopharmaceutical may have utility in radioisotope study of localized pathologic lesions. The scope of the invention is defined in the appended claims.

We claim:

1. A radiopharmaceutical for scintigraphic organ imaging comprising 2-mercaptoisobutyric acid labeled with reduced technetium-99m.

2. The radiopharmaceutical of claim **1** wherein the 2-mercaptoisobutyric acid is in aqueous solution and the technetium-99m is maintained in the reduced state by the presence of stannous tin.

3. A radiopharmaceutical consisting of mixed aqueous solutions of 2-mercaptoisobutyric acid and stannous chloride; and technetium-99m pertechnetate in physiological saline.

4. The radiopharmaceutical of claim **3** wherein the molar proportion of the 2-mercaptoisobutyric acid to stannous chloride is 3 to 1.

5. The method of making an instantly labeled liver specific radiopharmaceutical comprising the steps of

preparing a reagent of mixed aqueous solutions of 2-mercaptoisobutyric acid and stannous chloride; and

then adding to said reagent technetium-99m pertechnetate ions in physiological saline solution.

6. The method of serially imaging the liver and biliary tract of a patient comprising the steps of

preparing a radiopharmaceutical from 2-mercaptoisobutyric acid and technetium-99m maintained in the reduced state by the presence of stannous tin;

intravenously injecting the patient with said radiopharmaceutical; and then

scintigraphically imaging the liver and biliary tract to follow movement of radioactivity into the liver and then from it through the biliary tract.

7. The method of imaging localized pathologic lesions in a patient comprising the steps of

preparing a radiopharmaceutical from 2-mercaptoisobutyric acid labeled with reduced technetium-99m;

intravenously injecting the patient with said radiopharmaceutical; and

then scintigraphically imaging the lesion.

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