Technetium-99m-Labeled N-(2,6-Dimethylphenylcarbamoylmethyl) Iminodiacetic Acid (Tc-99m HIDA): A New Radiopharmaceutical for Hepatobiliary Imaging Studies

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An easily formulated, stable kit preparation of technetium-99m HIDA, suitable for use in humans, was developed and tested in mice and dogs. The tracer was cleared rapidly from the blood and excreted predominantly by the liver in both species. In dogs, the hepatobiliary clearance of Tc-99m HIDA was significantly greater than that of C-14 HIDA and Sn-113 HIDA. The LD_{50} for HIDA in mice, 168 mg/kg, exceeded the average human dose by a factor of 1000 on a per-weight basis. Blood clearance curves for Tc-99m HIDA in 12 normal subjects were biexponential with half-times of 4.6 ± 1.0 min and 31.5 ± 7.0 min, and cumulative 90-min urine samples contained 14.2 ± 1.8% of the injected dose. Images in normal subjects and nonjaundiced patients showed rapid concentration of tracer by the liver and activity was present within the biliary system in 10–20 min. In jaundiced patients, the tracer blood clearance was delayed and urinary excretion increased, but intestinal activity, indicating biliary patency, was imaged in those patients without complete focal obstruction of the common duct. Technetium-99m HIDA is a nontoxic radiopharmaceutical useful for clinical evaluation of hepatobiliary disorders in humans.

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N-(2,6-dimethylphenylcarbamoylmethyl) iminodiacetic acid (HIDA) is an N-substituted iminodiacetic acid structurally related to the drug lidocaine. The iminodiacetic acid moiety is a metal-chelating group, which allows the analog molecule to be radiolabeled with technetium-99m. The development of bifunctional radiopharmaceuticals based on N-substitution of iminodiacetic acid, and the chemical synthesis of HIDA, have both been reported previously (*1–4*). HIDA is produced easily by instant kit in a form that can be radiolabeled with technetium-99m. The resultant radiopharmaceutical has high radiochemical purity and is stable both in vitro and in vivo. Our studies show that Tc-99m HIDA is rapidly cleared from the blood and that its principal in vivo excretory pathway is via the liver and biliary tract.

This paper reports findings on the in vivo use of Tc-99m HIDA in animals, normal human subjects, and patients with liver disease. The results show that

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the radiopharmaceutical is eminently suitable for the study of gallbladder function and the clinical evaluation of hepatobiliary disease.

METHODS

Preparation of radiopharmaceutical. HIDA was synthesized by reacting equal molar amounts of ω-chloro-2,6-dimethylacetanilide and iminodiacetic acid in refluxing ethanol water (3:1) and was finally purified by recrystallization from water at pH 3.2 (*4*). The instant Sn HIDA kits were made by adding 0.2 ml of a $SnCl_2 \cdot 2H_2O$ solution (32 mg/ml, pH 1.0) to 320 mg of HIDA in its zwitterionic form contained in 32 ml of sterile water adjusted to pH 5.5–6.0. One milliliter of this solution was filtered through a 0.22-μ membrane filter* into each of 30 sterile pyrogen-free serum vials, which were lyophilized using a self-closing lyophilizer.† Each kit contained 10 mg of N-2,6-dimethylphenylcarbamoylmethyl) iminodiacetic acid and 0.2 mg of stannous chloride dihydrate. The kits were reconstituted by the addition of 1–3 ml of sterile sodium pertechnetate.

Samples of each lot of Sn HIDA were submitted in duplicate for sterility testing in thioglycolate media, and for pyrogen testing by the standard USP method. The stannous ion concentration was measured on the first, fifth, and seventh weeks using a standard potassium iodate/potassium iodide solution. The radiochemical purity of Tc-99m HIDA was determined by paper chromatography in physiological saline and paper electrophoresis for 1 hr in a 0.05*M* phosphate buffer, pH 6.8, at a constant voltage of 300 V, and was compared with controls of $^{99m}TcO_4^-$, Tc-99m DTPA, and Tc-99m Sn colloid. All paper strips were examined using a radiochromatogram scanner.

Animal studies. In mice and dogs the biodistribution and kinetic studies measured organ concentration as a function of time following injection, and also determined blood clearance curves and cumulative urinary excretion. Mice were injected with 0.1 ml of Tc-99m HIDA at a concentration of 15–60 mg/kg body weight and a specific activity of 10 μCi/cc; they were killed serially at intervals of from 1 min to 9 hr following injection. Two to six mice were used for each ordinate value. At the time of sacrifice the internal organs and carcasses were wet-weighed and their activity counted. Blood samples were collected in 0.1-ml capillary tubes that were rinsed with water into counting tubes. The absorbed radiation dose for humans was calculated using mouse distribution data and the absorbed radiation fractions and dose constants contained in the MIRD tables (*5,6*).

Thirty-two fasted mongrel dogs were anesthetized with 30 mg pentobarbital per kg body weight and were given intravenously one of: (a) 0.5 cc of Tc-99m HIDA at a concentration of 0.1 mg/kg body weight and a radioactive concentration of 4 mCi/cc; (b) 1.0 cc of [^{14}C] HIDA at a concentration of approximately 0.1 mg/kg body weight and a radioactive concentration of 4.8 μCi/cc; or (c) 0.7 cc of Sn-113 HIDA at a concentration of approximately 0.004 mg/kg body weight and a radioactive concentration of 9.1 μCi/cc. The [^{14}C] HIDA was prepared as previously described (*4*). The Sn-113 HIDA was prepared by adding 200 μCi of stannous Sn-113 ion to 0.2 cc of 10.5*N* HCl containing 5 mg of metallic tin. The mixture was heated to boiling until the tin dissolved, and 1.78 cc of water was added to bring the concentration of $SnCl_2$ to 4 mg/ml, pH 0. The stannous ion content was determined by titration with a standardized potassium iodate/potassium iodide solution, and was found to be 98% of its theoretical value. To 0.1 cc of $^{113}SnCl_2$ was added 1.0 cc of a 15 mg/ml solution of HIDA, so that the final solution contained 9.1 μCi Sn-113 HIDA/ml, pH 5.0.

Sequentially timed blood, urine, and bile samples were withdrawn from each animal using indwelling catheters, and the radioactivity of each sample was compared with a standard and expressed as a percentage of the injected dose.

Safety studies. The LD_{50} was determined in mice by the "up and down" sensitivity test, in which incremental higher or lower doses were administered depending upon the survival or death of the first animal injected (*7*). Male Swiss mice were used and carefully weighed for exact calculation of the mg/kg dose. The first test animal died upon receiving 0.4 ml HIDA at a concentration of 21 mg/ml. Forty mice were used to complete the test and received injections ranging from 0.1 to 0.4 ml of the same concentration of HIDA.

A long-term safety study was performed in two groups of six mice having an average weight of 15 g. The test group was injected with 1.3 mg of HIDA in 0.05 ml saline, a quantity equal to about 600 times the projected human dose on a per-weight basis. The control group was injected with an equal volume of physiologic saline. The test and control groups were compared by measuring the percent weight gain over a 2-week period.

Human studies. All normal human subjects and referred patients were studied under an approved protocol, including informed consent. The nine male and three female normal volunteers ranged in age from 22 to 41 years. Neither special patient preparation nor premedication was used. The baseline hematological and biochemical studies that were obtained

consisted of a complete blood count, total serum bilirubin, alkaline phosphatase, SGOT, SGPT, LDH, and CPK. These studies were repeated within 3 days, and again after an interval of 2 to 3 weeks. Blood pressure, pulse, and temperature were monitored during the initial phase of the study. The subjects were injected with 0.25 to 0.75 cc of Tc-99m HIDA at a concentration of 0.10 mg/kg body weight and a radioactive concentration of 4 mCi/ml. Sequential samples for blood clearance were obtained by means of an indwelling intravenous catheter up to 75 min following injection; after the final blood sample was obtained, the accumulated urine was collected. The specimens were counted and expressed as a percentage of injected dose.

Sequential images were obtained using a scintillation camera with a 140-keV diverging collimator. Each image on the day of injection contained 200,000 counts and was recorded on 35-mm film. The images were simultaneously recorded on tape through a data storage and analysis system or a computer. After the radiopharmaceutical had outlined the gallbladder, a drink of milk or eggnog was given and sequential images obtained. Late images of the abdomen containing 50,000–200,000 counts were collected 14–30 hr after injection. Anterior views of the liver and abdomen were obtained routinely and were supplemented by lateral or posterior views, as indicated, for organ localization.

Two categories of patients were studied. One group had a focal area of decreased activity on colloid liver scan in the region of the porta hepatis or in the inferior aspect of the liver. These patients were studied under the same protocol used for normal subjects. The remainder of the patients were jaundiced and received between 1.5 and 17.8 mCi of Tc-99m HIDA. Imaging studies in this group were performed sequentially up to 30 hr following injection.

RESULTS

Analysis of the Tc-99m HIDA kits showed no detectable pertechnetate anion or radiolabeled colloid. Paper electrophoresis of Tc-99m HIDA consistently yielded only one well-defined peak at a migration distance of 3.2 cm. Under identical conditions, $^{99m}TcO_4^-$, Tc-99m DTPA, and Tc-99m Sn colloid migrated 7.3, 5.1, and 0.0 cm, respectively. Over a 2-month observation period, the Tc-99m HIDA kits were stable, and tissue-distribution studies in mice showed no significant variations, with 78% of the injected dose present in the liver, biliary tract, and intestines by 30 min. Approximately 10% of the injected dose appeared in the urine. The blood clearance was rapid: only 3% of the injected activity remained in the blood at 5 min.

In dogs the blood clearance was less rapid, with 10% of the injected activity remaining in the blood at 10 min and 3% at 60 min. Average urinary excretion increased to 14% of the dose at 1 hr and 17% at 5 hr. Table 1 gives the percentages of Tc-99m HIDA, [^{14}C] HIDA, and Sn-113 HIDA recovered in the bile of dogs. Technetium-99m HIDA differs significantly from the other two radiochemicals in the rate and extent of its hepatobiliary clearance.

The LD_{50} for HIDA in mice was 168 mg/kg. No difference was detected in the percent weight gain between control groups and test groups used in the long-term safety study. The human radiation dosimetry for Tc-99m HIDA, as estimated from the mouse distribution data, gave a whole-body radiation dose of 0.021 rads/mCi, a liver dose of 0.023 rads/mCi, and an intestinal dose of 0.305 rads/mCi.

None of the subjects injected with Tc-99m HIDA spontaneously reported any symptoms, nor did questioning elicit symptoms that could be related to the

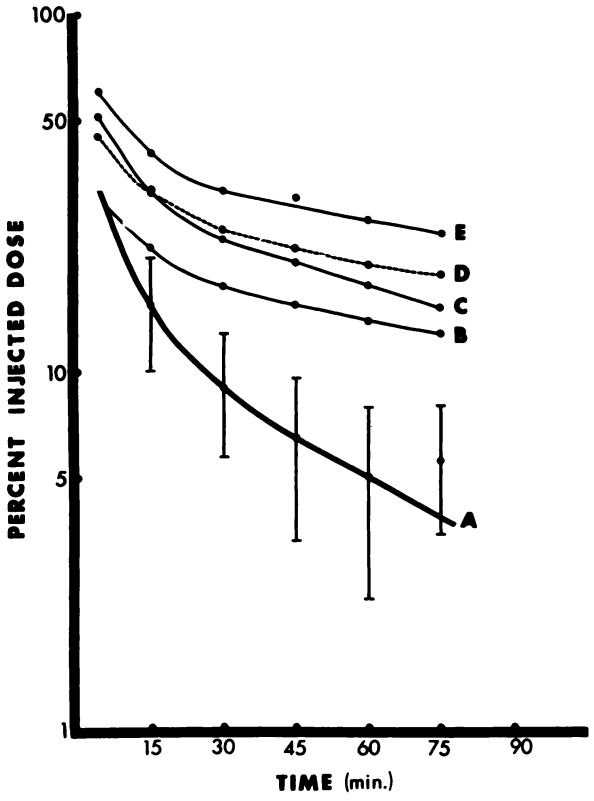

FIG. 1. Composite blood clearance curve of Tc-99m HIDA in 12 normal subjects (A) and four selected patients with jaundice. Serum bilirubin values (mg/dl): (B) 8.7, (C) 25.2, (D) 27.0, and (E) 4.2. Patient B had partial common-duct obstruction from pancreatic pseudocyst. Patient C had acute alcoholic liver disease (liver biopsy not done). Patient D had complete focal obstruction of common duct by external mass (at laparotomy, biopsy of lymph nodes did not show tumor). Patient E had alcoholic cirrhosis and ascites.

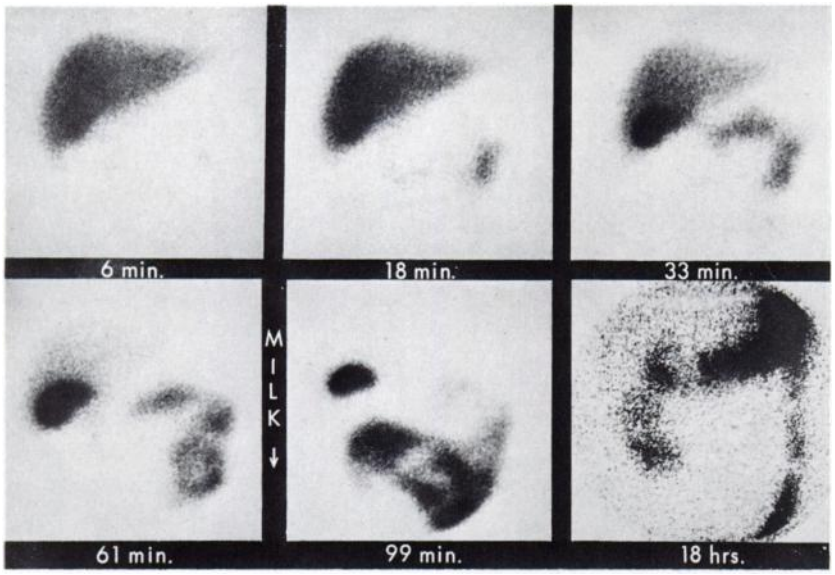

FIG. 2. Technetium-99m HIDA images in normal subject.

administration of the radiopharmaceutical. No significant change was noted in the vital signs measured during the initial phase of the study. There was no significant alteration of the hematological or biochemical parameters studied in the normal subjects, and in the patients changes noted in these parameters were consistent with the natural history of the disease under investigation.

The composite blood clearance curve for the 12 normal volunteers and four selected patients is shown in Fig. 1. After the initial mixing phase, the blood clearance curve for the normal subjects is biexponential, with half-times of 4.6 ± 1.0 min and 31.5 ± 7.0 min. The mean blood levels at 5 and 60 min were 32.0% ± 4.9 and 5.1 ± 2.8 percent of the injected dose. In the patients, the presence of jaundice was associated with an increase in the blood concentration of Tc-99m HIDA. In five selected jaundiced patients the mean values of the half-times for the blood clearance curve were 5.3 ± 0.7 min and 118 ± 36 min. In Fig. 1 are the blood clearance curves of four patients with jaundice of varying severity, who had either hepatocellular disease or common duct obstruction. As a group they are different from the normals, but there are no obvious features in these curves serving to distinguish either a patient with mild jaundice from one with severe jaundice or patients with hepatocellular disease from those with either partial or complete obstruction of the common duct.

In the 12 normal subjects, the mean cumulative 90-min urinary excretion of Tc-99m HIDA was 14.2 ± 1.8% of the injected dose. In ten patients with jaundice from various causes, the mean 90-min urinary excretion was 21.6 ± 12% of the injected dose and the mean cumulative 18- to 24-hr excretion in six of these patients was 52.8 ± 7% of the injected dose. Cumulative urines over 18–24 hr were not collected routinely in normal subjects because their urinary bladder time–activity curves indicated that urinary excretion was virtually complete in the first half hour (*8*); moreover, serial images showed no detectable renal activity after 30 min.

In the images of normal human subjects, liver activity appeared rapidly within a few minutes following injection (Fig. 2). By 10–20 min after injection, activity was present within the biliary system and subsequently was found either in the gallbladder or small intestines or in both. Gallbladder filling was observed in all subjects. Renal activity was frequently seen within the first 5–10 min but had disappeared by 30 min after injection. Following ingestion of milk or eggnog, gallbladder activity in some normal subjects diminished as gut activity increased, but this pattern of response was not observed in all subjects. The images obtained on the second day in all subjects reflected the passage of activity into the colon.

Figure 3 illustrates normal Tc-99m HIDA movement in a patient studied because the colloid liver scan showed a focal area of decreased activity in the region of the porta hepatis. The liver was readily visualized at 4 min and there was rapid passage of tracer into the biliary tract with subsequent accumulation in the gallbladder. In response to milk ingestion there was very rapid gallbladder contraction, with concurrent increase in activity in the small intestine. At 18 hr the activity was in the colon. Thus there was no evidence of biliary obstruction, and the area of decreased colloid accumulation by the

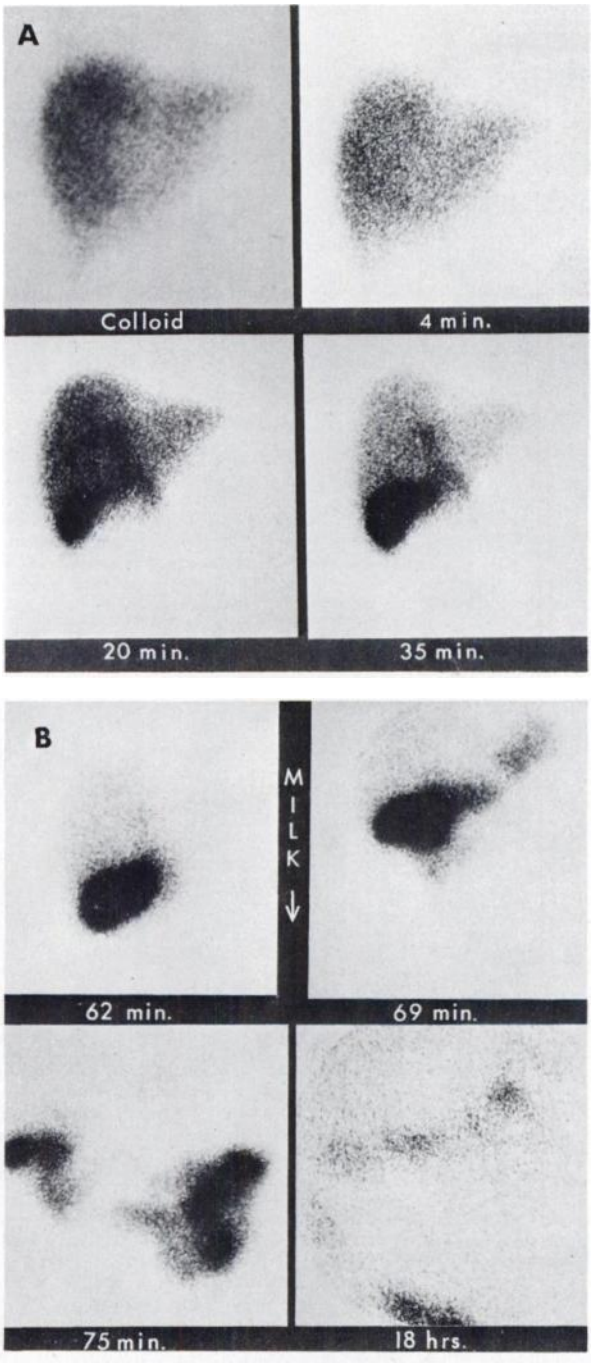

FIG. 3. Normal Tc-99m HIDA study in patient with focal area of decreased activity on colloid liver scan. A = Before milk ingestion; B = After milk ingestion.

Kupffer cells represented an anterior anatomic position of normal bile ducts within the liver substance.

Figure 4 shows a Tc-99m HIDA study in a mildly jaundiced patient with serum bilirubin of 2.6 mg/dl. Activity appeared rapidly in the liver and accumulated progressively in the gallbladder. Milk ingestion was followed by contraction of the gallbladder, increased intestinal activity, and, at 19 hr, accumulation in the colon. The cause of the jaundice was never determined in this patient, who was receiving chemotherapy for chronic lymphatic leukemia; one month later the bilirubin had decreased to 1.2 mg/dl. While the tracer was visualized in the blood pool and kidneys for a prolonged period of time, this study clearly demonstrated patency of the biliary tract with normal gallbladder motility, and effectively excluded significant disease of the gallbladder or biliary tract as the cause of the jaundice.

Figure 5 shows scintiphotos from a severely jaundiced patient with hepatocellular dysfunction and serum bilirubin of 18 mg/dl. The liver activity was well seen at 3 min but gradually diminished while right renal activity persisted on the images obtained up to 3 hr. Renal activity was differentiated from gallbladder activity on a right lateral view at 1 hr (not shown). Images at 19 hr showed activity within the intestinal tract (probably colon) and also in the bladder, indicating continuing renal excretion. The liver activity at 19 hr was diminished compared with intestinal activity, and neither the gallbladder nor biliary ducts were visualized. The presence of activity in the intestines indicated patency of the biliary drainage system. Other studies showed extensive recurrence of a poorly differentiated lymphoma in the chest and retroperitoneal space, without evidence of focal obstruction of the common duct, and the jaundice reflected diffuse liver involvement with the lymphoma. The patient had a rapid clinical and laboratory response to chemotherapy.

Figure 6 shows a Tc-99m HIDA study performed preoperatively in a jaundiced patient with serum bilirubin of 12 mg/dl, who was proven at laparotomy to have complete common-duct obstruction from cancer of the pancreas. Early in the study activity was seen in the cardiac blood pool, liver and kidneys, and a right lateral view at 1 hr (not shown) demonstrated that the focal density at the lower edge of the liver, seen at 25 and 58 min, was renal activity and not an accumulation of radiopharmaceutical in the gallbladder. There was no detectable activity in the gallbladder, biliary ducts, or intestines up to 27 hr after injection, consistent with complete obstruction to bile outflow.

DISCUSSION

Kinetic and imaging studies in humans paralleled the in vivo characteristics of Tc-99m HIDA in mice and dogs (*1,2*). A virtue of this agent is its rapid appearance in the biliary tract. Its other major attributes include suitability for "instant kit" formulation, low toxicity, and low absorbed radiation dose. The high radiochemical purity exhibited by Tc-99m HIDA precludes interference with the image analysis by radiocolloid or pertechnetate. Based upon tissue-

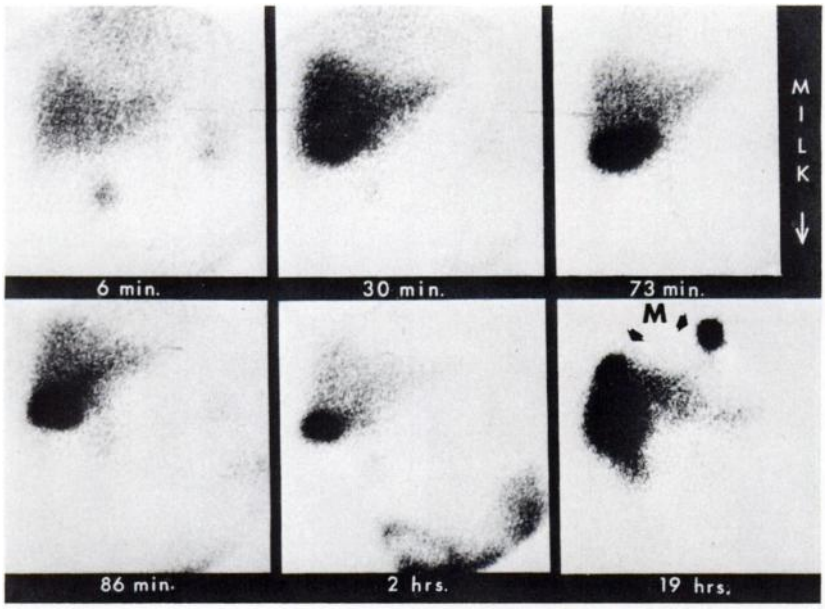

FIG. 4. Technetium-99m HIDA study in patient with bilirubin of 2.6 mg/dl and no evidence of biliary disease. At 19 hr, activity is only in the colon [two markers (M) indicate right costal margin].

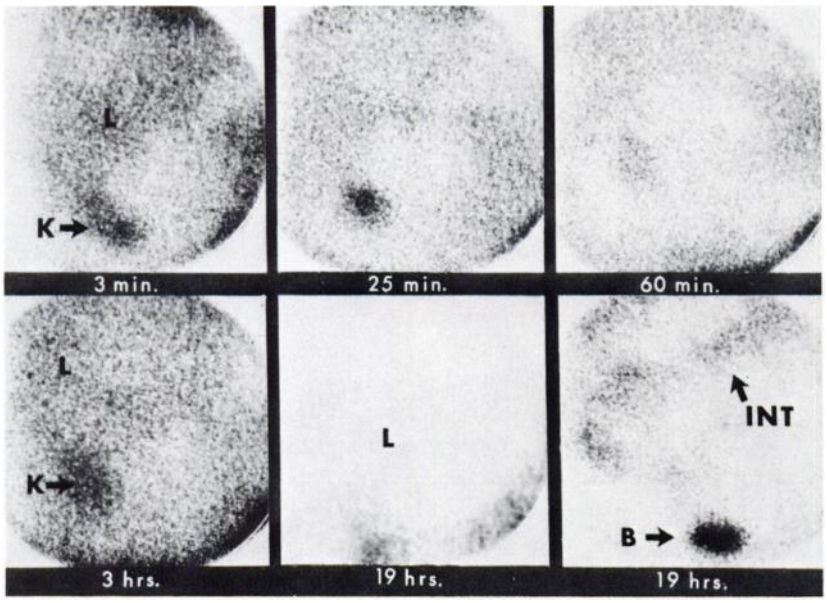

FIG. 5. Technetium-99m HIDA study in jaundiced patient with hepatocellular dysfunction and serum bilirubin of 18 mg/dl. On day 1 activity is present in liver (L) and right kidney (K) (left renal outline is obscured). At 19 hr, upper-abdominal image shows decreased liver (L) activity, while lower-abdominal image shows activity in intestines (INT) and bladder (B).

distribution studies in mice, the radiation dose per millicurie for Tc-99m HIDA is small compared with that for [^{131}I] rose bengal (*9*). Extrapolation of mouse data to man, however, introduces several errors into the human dosimetric estimates. Thus, although the extent of the hepatobiliary clearance of Tc-99m HIDA appears similar in man and mouse, the rate of its clearance in man is retarded, resulting in an increased human radiation dose. Further, large changes in both the extent and rate of Tc-99m HIDA clearance have been observed in patients with hepatobiliary disease. Although the use of these factors will not significantly alter the conclusions concerning the low radiotoxicity of Tc-99m HIDA in humans, new dosimetric estimates should be made, using time–activity curves with the disease state as parameter. This work is currently in progress.

Although HIDA and Tc-99m HIDA have different biological distributions, as indicated by the data in Table 1, the safety and toxicity studies in animals were performed with HIDA because it is the major chemical constituent of Tc-99m HIDA. The LD_{50} for HIDA in mice (168 mg/kg) is between 1,000 and 1,500 times the administered human dose on a per-weight basis. In normal human subjects receiving injections of Tc-99m HIDA that contained 0.1 mg of HIDA per kilogram of body weight, sequential studies up to 3 weeks failed to reveal any significant changes in the hematological or biochemical parameters studied. Since there is a large difference in

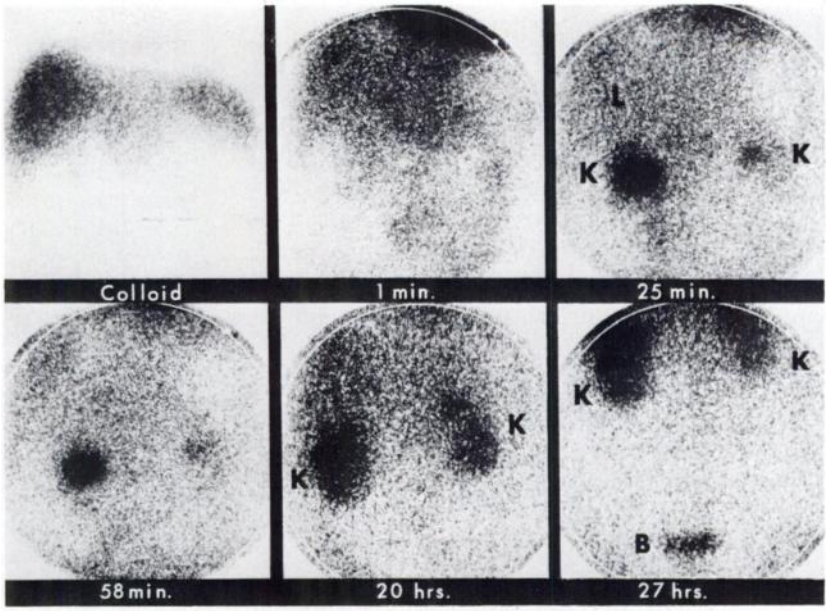

FIG. 6. Preoperative Tc-99m HIDA study in a jaundiced patient with serum bilirubin of 12 mg/dl who had complete common-duct obstruction from cancer of the pancreas. Colloid scan is normal. Technetium-99m HIDA excretion by kidneys (K) rapidly makes them more prominent than liver (L) on day 1. No intestinal activity is seen up to 27 hr, but continuing renal excretion outlines bladder (B) at 27 hr.

hepatobiliary clearance between Tc-99m HIDA and either HIDA or Sn-113 HIDA, as shown in Table 1, the clearance of Tc-99m HIDA is independent of the HIDA present in the administered dose.

The kinetic data showed that the distribution phase of the Tc-99m HIDA blood clearance curve did not vary significantly between normal subjects and jaundiced patients, whereas the elimination phase was significantly prolonged in the jaundiced patients. From visual inspection of the curves, it was possible to distinguish neither the severity of the jaundice nor the type of disease-causing jaundice, nor could the levels of urinary activity be used to identify the cause of jaundice since increased renal extraction occurred with all types of jaundice.

In normal human subjects and nonjaundiced patients, the rapid liver concentration and transport of Tc-99m HIDA provided excellent sequential images of the hepatobiliary system. We note that gallbladder filling was achieved with Tc-99m HIDA in all normal subjects whether they fasted or not. Use of a cholecystogogue to empty the gallbladder before an imaging study has been advocated (*10*) and requires further clarification with regard to Tc-99m HIDA.

In the mildly jaundiced patient, although the liver concentration and transport of Tc-99m HIDA were less rapid than in normal subjects, the biliary tract was adequately outlined in sequential views. In severely jaundiced patients the liver and biliary system were not well seen compared with normal studies, and the gallbladder was not visualized whenever serum bilirubin levels exceeded 10 mg/dl for any reason. When the biliary system was patent, however, images of the abdomen showed activity in the intestines, while no intestinal activity was found in patients with complete biliary obstruction. Through reduction of general background activity, the significant renal excretion that occurred at elevated bilirubin levels was helpful in allowing detection of small amounts of localized intestinal activity. In severely jaundiced patients without complete biliary obstruction, however, the small amount of Tc-99m HIDA cleared through the liver into the intestines may not be visualized on the first day because of the high body background, but by the second day the continuing renal excretion reduces the background enough so that small quantities of intestinal activity, located principally in the colon, may be detected in images containing 200,000 counts. We therefore modified the dose of administered radiopharmaceutical according to the level of jaundice. In most patients, 6–10 mCi provided adequate images at

TABLE 1. HEPATOBILIARY EXCRETION OF Tc-99m HIDA [^{14}C] HIDA, AND Sn-113 HIDA

Time (min)	Percent injected dose in bile		
	Tc-99m HIDA*	Sn-113 HIDA†	[^{14}C] HIDA‡
0–15	3.5	0.006	0.004
15–30	18.4	0.005	0.010
30–45	17.3	0.002	0.047
45–60	16.1	0.002	0.061
60–90	15.7	—	0.031
Total	71.0	0.015	0.153

* Mean of three dogs.
† Mean of two dogs.
‡ Mean of two dogs.

18 hr, but with bilirubin levels in the range of 15 mg/dl or higher, a dose of 10–15 mCi proved more satisfactory for imaging on the second day. It was important to use a right lateral view to distinguish gallbladder activity from renal activity when the patient was significantly jaundiced, and this view was obtained routinely at approximately 1 hr and compared with subsequent images. In some patients, posterior views were used to identify the outlines and thereby to distinguish between renal and intestinal activity on the anterior views.

In normal subjects and in patients with a variety of hepatobiliary diseases, Tc-99m HIDA provided high-quality scintiphotos of the liver and biliary system, and it effectively evaluated biliary patency in severely jaundiced patients, although the quality of liver and biliary images was reduced compared with nonjaundiced patients. In this initial study, however, Tc-99m HIDA did not distinguish hepatocellular disease from partial common duct obstruction with continued biliary excretion into the gut, a finding that has been encountered previously in the evaluation of hepatocyte imaging agents (*11,12*).

Based on these results, we feel that further studies of the clinical usefulness of Tc-99m HIDA are warranted, including the evaluation of the potential efficacy of combining Tc-99m HIDA with other diagnostic modalities such as ultrasound in the evaluation of patients with hepatobiliary disease (*13*).

FOOTNOTES

* Millipore Corporation, Bedford, Mass.

† Virtus model No. 10-800.

ACKNOWLEDGMENTS

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