

**Hepato-Biliary Scintigraphy and Hepatography with
Tc-99m Diethyl-Acetanilido-Iminodiacetate
in Obstructive Jaundice**

S. Pors Nielsen, J. Trap-Jensen, J. Lindenberg, and M. Lykkegard Nielsen

Frederiksberg Hospital, Copenhagen, Denmark

Tc-99m diethyl-IDA was used for combined serial hepato-biliary scintigraphy and processing of hepatographic curves, using a scintillation camera and an image-processing system. Patients with obstruction of the common bile duct, proven by operation, were investigated. Hepatograms from an area of interest corresponding to the periphery of the right liver lobe varied predictably with changes in the serum levels of alkaline phosphatase and bilirubin. Both anatomical and functional information was obtained. The investigation could be carried out even under reduced liver function. Hepatic uptake of the agent was noted at serum alkaline phosphatase levels up to 1000 U/l and serum bilirubin levels up to 170 μ mol/l.

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The new Tc-99m-labeled radiopharmaceuticals based on N-substitution of iminodiacetic acid (1,2) are potentially useful in the diagnosis and grading of obstructive biliary disease. Among their advantages are the following: (a) they are quickly taken up by the hepatocytes and excreted into the bile; (b) they are ideal for scintillation-camera imaging; (c) they are inexpensive and can be used without side effects or discomfort to the patient, and (d) they may be used in jaundiced patients in whom radiologic contrast methods are useless. Their future clinical use might depend on the solution to the following two questions: (a) can serial hepato-biliary scintigraphy be transformed into a quantitative excretory liver function test; and (b) can patients with significant obstruction of the common bile duct be investigated?

This paper is an attempt to answer these questions. It reports our experiences with an iminodiacetic acid derivative, used in patients with obstructive hepato-biliary disease. For the purpose we have used Tc-99m diethyl-acetanilido-iminodiacetate (Tc-99m diethyl-IDA) available commercially as a stable preparation from an instant stannous kit.

METHODS

Tc-99m diethyl-IDA was injected intravenously at a dose level of 75 μ Ci Tc-99m per kilogram body weight, containing a total of 40.2 mg diethyl-IDA. Polaroid scintiphotos were made, in a supine position, every 4 or 5 min for 30 min (in some cases for 40, 50, or 60 min) using a scintillation camera, collimated with parallel holes. Histogram-mode 64 \times 64 images were recorded at 10-sec intervals. They were stored on the disk of a computerized image-processing system. Display was made from the stored records. Rectangular regions of interest (all equal in area) were flagged, corresponding to the peripheral portion (about 1/4) of the right hepatic lobe, the gallbladder, the abdominal aorta, or the heart. Time-activity curves (hepatograms) were then computed and printed out with a Teletype line printer, the curves being derived from the count rates (also printed out) for the 10-sec intervals.

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For reprints contact: S. Pors Nielsen, Dept. of Clinical Physiology, Frederiksberg Hospital, DK-2000 Copenhagen F, Denmark.

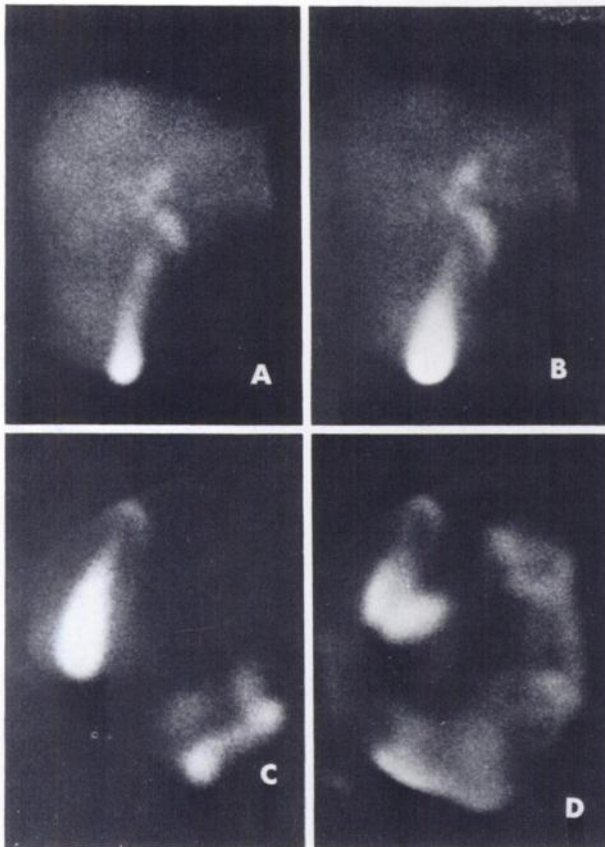


FIG. 1. Hepato-biliary scintigraphy with Tc-99m diethyl-DIA in a normal fasting subject (A, B, C) 20, 40, and 70 min after injection, respectively. Emptying of the gallbladder was induced by drinking a glass of cream with two egg yolks 71 min after injection. The situation 7 min later is illustrated in (D).

Calculations. The hepatic uptake of Tc-99m diethyl-IDA was assessed by means of an "uptake index," obtained by taking the ratio of the activity in the flagged area in the right hepatic lobe over that for the aorta—both at 3 min postinjection. The liver's excretory capacity was measured by a "retention index," defined as the ratio of the activity in the right-lobe area at 30 min over the same at its maximum. These ratios were correlated with the serum concentrations of bilirubin and alkaline phosphatase (normal values 5–17 $\mu\text{mol/l}$ and 50–275 U/l, respectively).

Patients and normal subjects. A total of 7 normal subjects and 34 patients with obstructive hepato-biliary disease, proven by operation, were studied. Informed consent was obtained from both groups. Among them, 20 patients and the seven normal subjects had significant hepatic uptake of Tc-99m diethyl-IDA. In the remaining 14 patients, jaundice was so pronounced that no hepatic uptake or excretion could be observed.

All but four studies were performed after 6 hr of fasting.

RESULTS

Scintiphotos. Normal subjects. In normal fasting subjects and patients with moderate biliary obstruction, the liver and the heart are seen equally well at 1–3 min after i.v. injection. After that time the heart image fades and the liver becomes more clearly visible, reaching maximum intensity at about 10 min after injection. Delineation of the gallbladder and the common bile duct (and eventually the duodenum) is clear 20–30 min after the injection.

Shortly after a meal, the hepatic uptake, excretion into the bile, and the flow of bile through the common bile duct are all increased, and visualization of the liver is clearer than in the fasting state. Conversely, the gallbladder is best seen during a fast.

A series of scintiphotos from a normal fasting subject is shown in Fig. 1. They include an image taken 7 min after the subject drank a glass of cream with two egg yolks.

Patients with biliary obstruction. In patients with moderately elevated serum levels of bilirubin and alkaline phosphatase, enough anatomical information is obtained by serial hepato-biliary-scintigraphy for 30 min. In cases of suspected pronounced biliary obstruction, it is advisable to extend the investigation to a total of 50 or 60 min. Complete obstruction of the common bile duct can be diagnosed by the ab-

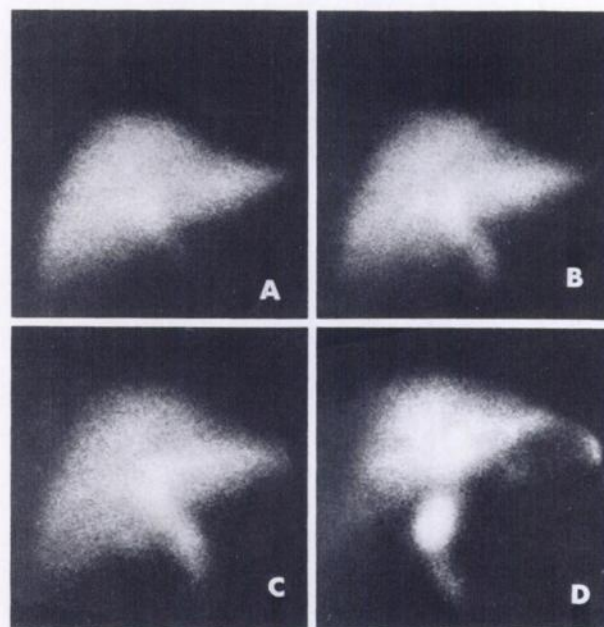


FIG. 2. Hepato-biliary scintigraphy with Tc-99m diethyl-IDA in a patient with stones in the gallbladder and common bile duct: (A, B, C) 20, 30, and 40 min after injection, respectively. Postoperative visualization of site of choledochoduodenostomy 40 min after injection (D).

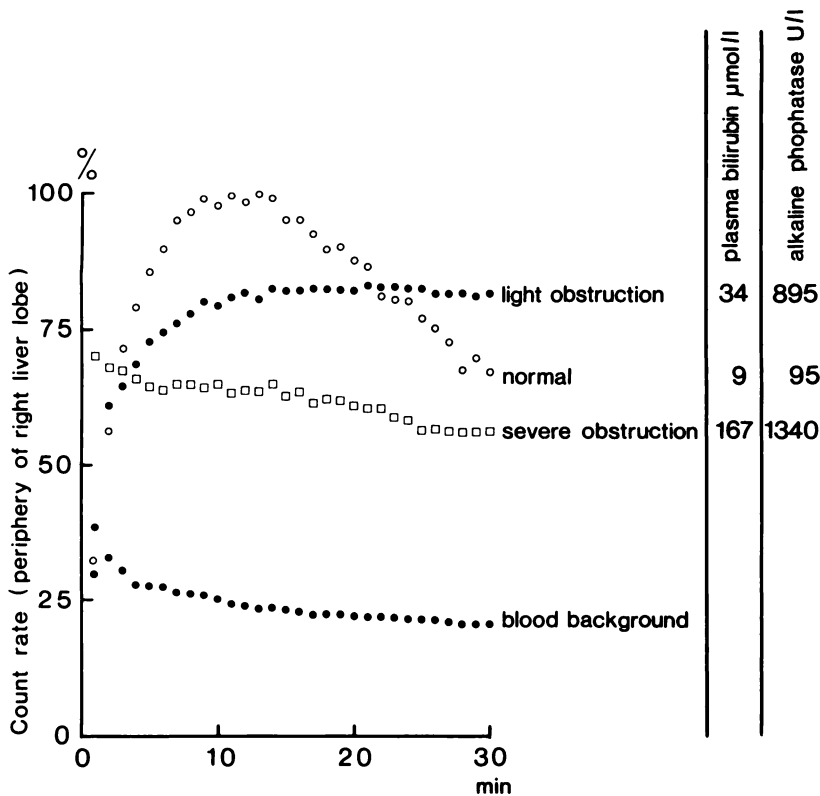


FIG. 3. Hepatograms from a areas of interest of identical size over peripheral part of right liver lobe, in three subjects with different degrees of obstruction of the common bile duct. Middle curve (light obstruction) is hepatogram corresponding to the scintigrams of Fig. 2 (A, B, and C).

sence of intestinal radioactivity 24 hr after injection.

Figure 2 shows scintiphotos from a patient with stones in the common bile duct and gallbladder, illustrating the absence of tracer from the duodenum and the gallbladder after 30 and 40 min, and pileup of radioactivity at the porta hepatis (central intrahepatic bile ducts) and the upper part of the common bile duct. A postoperative scintigram (Fig. 2D) clearly shows an anastomosis between common bile duct and duodenum.

Failure of the gallbladder to fill 30 min after injection in the fasting patient was shown by operation to indicate either gallbladder disease or pronounced obstruction of the common bile duct.

Hepatograms. In a normal fasting subject, the time-activity curve of an area of interest corresponding to the periphery of the right liver lobe has a maximum around 10 min after injection. There after the curve declines (Fig. 3), reaching a value of about 60% of the maximum at 30 min after injection. In the presence of mild biliary obstruction, the following changes (same area of interest) can be observed: (a) the maximum is lower; (b) the maximum occurs later, if ever; and (c) the 30-min level differs little from the maximum. In severe obstruction, with total occlusion of the common bile duct, the curves become very like those for "blood background"—from the abdominal aorta or the heart (Fig. 3).

The *uptake index* decreased with increasing levels of serum bilirubin and alkaline phosphatase (Fig. 4, top).

The *retention index* increased with increasing serum bilirubin and alkaline phosphatase, reaching 1.0 (horizontal or continuously rising curve) with alkaline phosphatase concentrations of about 1000 U/l (Fig. 4, bottom) and/or a serum bilirubin level of about 170 $\mu\text{mol/l}$. In the following we have termed these values of serum alkaline phosphatase and bilirubin as "the biochemical limit." Not surprisingly, the *retention index* was lower in nonfasting patients, in whom bile flow is increased.

Table 1 demonstrates that successful operative relief of common bile duct obstruction is followed by changes of uptake index and retention index toward normal values.

Time-activity curves corresponding to the gallbladder have been processed in the fasting state and after a fatty meal with eggs. They seem to be of diagnostic value in the diagnosis of gallbladder disease, including cholecystolithiasis. However, the normal gallbladder curves exhibit a great variety of filling and emptying patterns, the study of which has not yet been completed.

Degree of jaundice. It can be seen in Fig. 3 that patients with serum alkaline phosphatase over 1,000 U/l and/or serum bilirubin over 170 $\mu\text{mol/l}$ had an

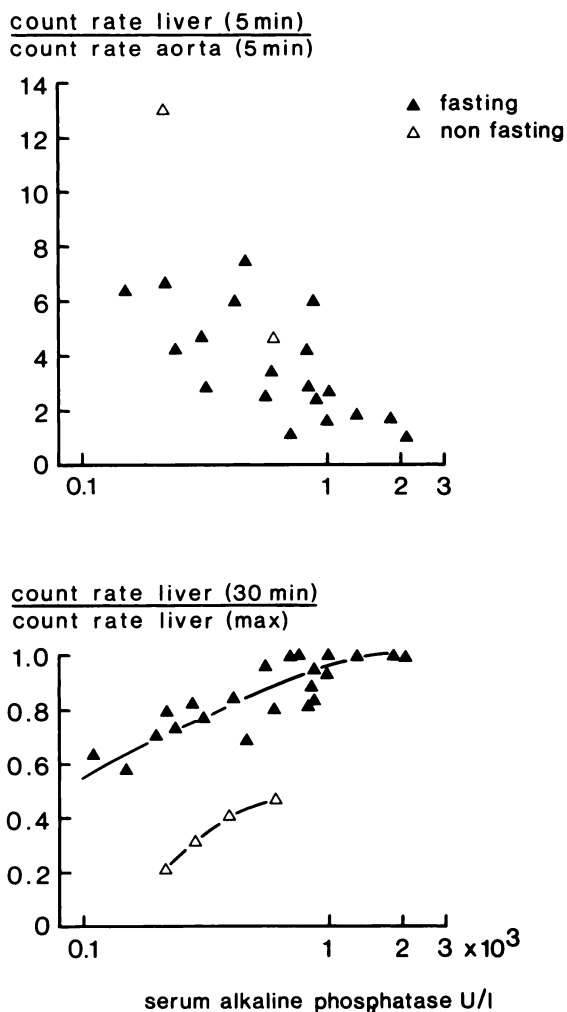


FIG. 4. Hepatic uptake index (above) and hepatic retention index (below) in normal subjects and patients with varying degrees of obstruction of common bile duct, as judged by serum alkaline phosphatase (maximum 2,200 units/l).

uptake index approaching zero and an retention index around unity, indicating that hepatic uptake and excretion of Tc-99m diethyl-IDA were insignificant. Below this "biochemical limit" the hepatograms had a definite uptake phase. Scintillation images grew fainter at increasing levels of serum alkaline phosphatase and bilirubin. However, clear images of the liver were produced even above this limit (14 patients). Liver images obviously were then due to the relatively high blood flow in the liver. Above the "biochemical limit," Tc-99m diethyl-IDA, giving only structural information (e.g., filling defects), is not superior to sulphur colloid agents. At nearly total obstruction of the common bile duct (stone in the duct or carcinoma of the head of the pancreas) a fan-shaped filling defect can sometimes be seen in the portal region of the liver. The presence of such a defect probably indicates dilated central intrahepatic

bile ducts, and might be of importance for the differential diagnosis between obstructive jaundice and jaundice caused by parenchymatous liver disease.

In severely jaundiced patients, the evaluation of the camera images is sometimes hampered by excretion of the radioactivity into the kidneys. In particular, the right kidney can create difficulties for the evaluation of the portal and gallbladder regions. Below "the biochemical limit," however, the problem is negligible.

Visualization of the gallbladder. Analysis of our material demonstrates that the presence or absence of gallbladder function was correctly predicted by Tc-99m diethyl-IDA serial hepato-biliary scintigraphy, as long as the liver function was sufficient for hepatic uptake of Tc-99m diethyl-IDA (patients below "the biochemical limit"). This is illustrated in Table 2, which also demonstrates that radiologic contrast investigations would be needed in a smaller number of cases than those favorable to study with Tc-99m diethyl-IDA.

DISCUSSION

Technetium-99m-diethyl-IDA in animal studies (baboons) proved to exhibit relatively prominent hepatic uptake and biliary excretion, together with very moderate urinary losses, compared with other Tc-99m-labeled hepato-biliary agents and [¹³¹I] rose bengal (2). According to the manufacturer, the LD₅₀ in mice for diethyl-IDA is 280 mg/kg body weight, this being in the same order of magnitude as the LD₅₀ for N-(2,6-dimethylphenyl carbamoylmethyl) iminodiacetic acid (3).

Tc-99m diethyl-IDA promises to be the best, or one of the best, hepato-biliary radiopharmaceuticals to date. Yet no extensive report concerning the clinical usefulness of this radiotracer has appeared, and the role of Tc-99m diethyl-IDA in the daily clinical routine remains unclarified (4).

This paper shows that:

1. The imaging of the liver, the main intrahepatic and the extrahepatic bile ducts, and the gallbladder is satisfactory with Tc-99m diethyl-IDA in obstructive hepato-biliary disease up to a certain limit.
2. Time-activity curves corresponding to the periphery of the right lobe of the liver vary predictably with the serum levels of alkaline phosphatase and bilirubin in extrahepatic biliary tract obstruction.

The procedure of combined serial hepato-biliary scintigraphy and time-activity curve processing supplies both structural and functional information. The described procedure is a parallel to the combined serial scintigraphy of the kidneys and renography with Tc-99m DTPA, as developed in our department (5).

TABLE 1*

Patient No.	Diagnosis	Operation		Serum bilirubin $\mu\text{mol/l}$	Serum alkaline phosphatase U/l	Uptake index	Retention index
1	Stones in common bile duct	Choledocholithotomy	Before operation	34	895	6.11	0.87
			After operation	6	220	6.61	0.79
2	Stones in gall-bladder and common bile duct	Cholecystectomy, choledocholithotomy, choledochoduodenostomy	Before operation	85	561	2.50	0.96
			After operation	40	310	4.70	0.78
3	Cancer of the head of pancreas	Cholecystojenunostomy	Before operation	175	1880	1.71	1.00
			After operation	119	900	2.55	0.95

* Three patients with different degrees of obstruction of common bile duct. Effect of operation on serum bilirubin and alkaline phosphatase, and on uptake index and retention index of hepatograms from an "area of interest" corresponding to periphery of right liver lobes. Values immediately before operation and 2 wk after operation.

The quantitative evaluation of hepatic uptake and biliary excretion of Tc-99m diethyl-IDA, as described by hepatograms from a region of interest over the periphery of the right liver lobe, as still incomplete. A more precise and accurate quantitative test of the liver's excretory function with this radiopharmaceutical, taking into account the moderately declining blood background and renal excretion, awaits the results of kinetic studies in man and the elaboration of a biologically relevant kinetic model. The fact that hepatic uptake and excretion take place even with high serum levels of alkaline phosphatase and bilirubin, when radiologic contrast methods cannot be applied, suggests that a useful quantitative excretory liver function test might be developed along the lines described in this paper.

The blood background decreased by around 10% for the first 30 min. Subtraction of this background did not change any of the conclusions.

As mentioned, the gallbladder is most clearly visualized in the fasting state, and the common bile duct is often easier to see when bile flow is high—e.g., after meals—than when it is low. Therefore, in a case of suspected gallbladder disease, the patient should be investigated in the fasting state, as suggested for scanning with Tc-99m pyridocylidene-glutamate (6). In a case of suspected common bile duct obstruction it might be advisable to carry out the investigation shortly after a meal in order to stimulate bile flow. This would facilitate the location of a possible obstruction.

The anatomical information derived from Tc-99m diethyl-IDA cholescintigraphy is less detailed, for obvious reasons, than that of radiologic methods, when the latter can be performed.

It is possible, however, that hepato-biliary scintigraphy can become a valuable diagnostic aid in cases of obstruction so severe that radiologic contrast

TABLE 2*

Diagnosis	Radiology: Number of patients in whom oral cholecystography and/or i.v. cholangiography could be carried out	Scintigraphy: Number of patients in whom cholescintigraphy was carried out	Number of patients with visible gallbladder by cholescintigram
I No hepatobiliary disease	7	7	7
II Stone(s) in common bile duct with normal gallbladder, proven by operation	0	2	0 (severe obstruction, near "biochemical limit")
III Stone(s) in gallbladder with or without stone(s) in common bile duct, proven by operation	5	7	0
IV After cholecystectomy	Not attempted	7	0
V After cholecystojenunostomy	Not attempted	4	4

* Patients with hepatic uptake of Tc-99m diethyl-IDA (serum levels of alkaline phosphatase and bilirubin below 1,000 U/l and 150 $\mu\text{mol/l}$, respectively). Predictive value of visible/nonvisible gallbladder of Tc-99m diethyl-IDA cholescintigraphy. Radiologic contrast examinations could not be carried out in all patients, but gave the correct diagnosis when carried out.

methods are useless, or if the patient is sensitive to contrast media, as often happens after i.v. cholangiography (4).

Preliminary studies in our laboratory suggest that absence of radioactivity in the intestines 24 hr after administration might be a sign of complete occlusion of the common bile duct.

The method is invariably useful for the demonstration of a functioning cholecysto-jejunostomy, cholecysto-duodenostomy, or choledochoduodenostomy. Radiologic contrast methods are less favorable for such purposes due to low contrast intensity at the sites of anastomosis. Present work in this laboratory aims at establishing whether subtotal stricture of a biliary-intestinal anastomosis can be reliably diagnosed with the method.

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REFERENCES

1. LOBERG MD, COOPER M, HARVEY E, et al: Development of new radiopharmaceuticals based on N-substitution of iminodiacetic acid. *J Nucl Med* 17: 633-638, 1976
2. WISTOW BW, SUBRAMANIAN G, VAN HEERTUM RL, et al: An evaluation of ^{99m}Tc-labeled hepatobiliary agents. *J Nucl Med* 18: 455-461, 1977
3. RYAN J, COOPER M, LOBERG M, et al: Technetium-labeled N-(2,6-dimethylphenylcarbonylmethyl)iminodiacetic acid (Tc-99m HIDA): A new radiopharmaceutical for hepatobiliary imaging studies. *J Nucl Med* 18: 997-1004, 1977
4. RONAI PM: Hepatobiliary radiopharmaceuticals: defining their clinical role will be a galling experience. *J Nucl Med* 18: 488-490, 1977
5. NIELSEN SP, MØLLER ML, TRAP-JENSEN J: ^{99m}Tc-DTPA scintillation-camera renography: a new method for estimation of single-kidney function. *J Nucl Med* 18: 112-117, 1977
6. BAKER RJ, MARION MA: Biliary scanning with Tc-99m pyridoxylidene-glutamate—The effect of food in normal subjects: Concise communication. *J Nucl Med* 18: 793-795, 1977

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