Tc-99m-Diethyl-IDA Imaging: Clinical Evaluation in Jaundiced Patients

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Hepatobiliary imaging with Tc-99m-N,α-(2,6-diethylacetanilide)-iminodiacetic acid (Tc-diethyl-IDA) was performed in 91 jaundiced patients with documented hepatobiliary damage and serum total bilirubin up to 35 mg/dl. There were 56 patients with obstructive jaundice and 35 with hepatocellular disease. Correct discrimination between hepatocellular and obstructive jaundice was possible with an overall accuracy of 90%. Agreement with the final clinical diagnosis was obtained in 97% of patients with hepatocellular disease, and in 86% of patients with obstructive jaundice. The reliability of the test was inversely related to the serum bilirubin concentration. The incidence of true-positive scans dropped from 93% for bilirubin levels below 10 mg/dl to 83% for bilirubin between 10 and 20 mg/dl. Above 20 mg/dl, the demonstration of a mechanical obstruction was possible in only one out of the four patients with obstructive jaundice. The high predictive values of the test illustrate that Tc-diethyl-IDA imaging constitutes a reliable method to demonstrate an obstructive cause for the jaundice as long as the bilirubin level remains below 20 mg/dl.

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During investigation of a jaundiced patient, an important step is to determine whether the icterus is of hepatocellular or mechanical origin. Clinical and biological data generally allow one to answer this question. However, when more information is needed, several noninvasive techniques remain available, one of which is gamma imaging.

For many years, radioiodinated rose bengal has been used as the hepatobiliary agent (*1*). Recently, various substituted iminodiacetic acids, labeled with Tc-99m have been developed and proposed for the investigation of the hepatobiliary system (*2*). The main advantages of these compound are an easy labeling with technetium and rapid hepatic uptake and excretion (*3*). Several aspects of the usefulness of the IDA derivatives have already been evaluated in various hepatobiliary disturbances (*4–11*). In the present study, a large group of jaundiced patients has been investigated in order to assess the ability of Tc-diethyl-IDA imaging to distinguish between hepatocellular and obstructive jaundice.

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MATERIALS AND METHOD

Ninety-one jaundiced patients were investigated. These included 35 with hepatocellular disease and 56 with obstructive jaundice (Table 1). No patients with hepatocellular disease and superimposed obstruction were encountered in this study. Serum total bilirubin levels ranged from 1 to 35 mg/dl (normal value < 1 mg/dl).

The final diagnosis was obtained by other methods, such as oral cholecystogram, intravenous cholangiogram, endoscope retrograde cholangiography and pancreatography (ERCP), laparoscopy, and hepatic biopsy. In some cases the diagnosis was either obtained or confirmed by surgery.

The labeling of the tracer was achieved by adding a pyrogen-free sterile [^{99m}Tc]pertechnetate solution (10–30 mCi; 1–4 ml) into a vial containing 40.2 mg of

TABLE 1. PATIENTS SCINTIGRAPHED WITH Tc-DIETHYL-IDA

Final clinical diagnosis		Serum bilirubin <10 mg/dl	10–20 mg/dl	>20 mg/dl
Hepatocellular disease:	cirrhosis (23)	15	4	4
	hepatitis (9)	7	2	0
	metastatic liver (2)	0	1	1
	septicemia (1)	0	1	0
Obstructive jaundice:	tumor of pancreas (16)	7	6	3
	bile-duct carcinoma (11)	6	4	1
	choledocholithiasis (14)	14	0	0
	cholangitis (5)	5	0	0
	cholecystitis (4)	4	0	0
	bile-duct ligation (2)	1	1	0
	odditis (2)	2	0	0
	gallbladder carcinoma (1)	1	0	0
	metastatic liver (1)	0	1	0
Total (91)		62	20	9

commercial N,α-(2,6-diethylacetanilide)-iminodiacetic acid. The colorless solution containing the end product had a final pH of 5.5. Paper electrophoresis (barbital buffer, pH 8.6, 400 V for 2 hr at 4°C) indicated that 87.7% of the radioactivity corresponded to Tc-diethyl-IDA, with less than 2% of free pertechnetate.

The equipment and techniques used have been described previously (7). After overnight fasting, the patients were injected intravenously with a standard dose of 5–8 mCi of Tc-diethyl-IDA. Using a scintillation camera, serial abdominal views were obtained during the first hour at least and, if necessary, up to 24 hr.

The scintigraphic findings were read and classified using the following criteria: (a) the quality of the early hepatic uptake; (b) the quality of the late parenchymatous discharge; (c) the degree of tracer concentration in the bile ducts; and (d) the bowel visualization (Fig. 1).

According to these criteria, the patients were classified into various groups.

1. Hepatocellular disease: characterized by decreased hepatic uptake, delayed hepatic discharge and bowel visualization, and no stasis of the tracer in the bile ducts (Fig. 2A). A second pattern of hepatocellular disease is characterized by little or no hepatic uptake, with consequent failure of bowel or bile-duct visualization (Fig. 2B).

2. Incomplete mechanical obstruction: good hepatic uptake, delayed hepatic discharge and bowel visualization, and stasis of the tracer in the bile ducts (Fig. 3A).

3. Complete mechanical obstruction: well-preserved hepatic uptake, little or no hepatic discharge, and no visualization of bile ducts or bowel (Fig. 3B).

All scans were interpreted by two different observers without knowledge of the clinical and biological findings. Values are expressed as mean ± s.d. The Student's t-test was used in the statistical analysis of the data.

RESULTS

Table 2 summarizes the main scintigraphic findings.

Patients with hepatocellular disease. In six patients, all with serum bilirubin values above 10 mg/dl, no hepatic uptake, bile-duct visualization, or gut activity could be demonstrated (Tables 2 and 3).

In the 29 remaining patients, hepatic uptake was decreased and was inversely related to the bilirubin level. Hepatic uptake was well preserved in 21 of the 23 patients with bilirubin values below 10 mg/dl, but was never observed with bilirubin above 10 mg/dl (Table 3

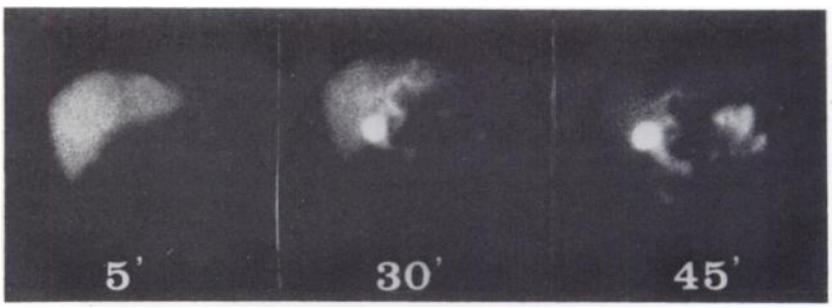

FIG. 1. Normal subject. Fifth min, clear visualization of the liver; 30th min, gallbladder filling, bile-duct visualization without stasis, duodenal passage; 45th min, good parenchymatous discharge.

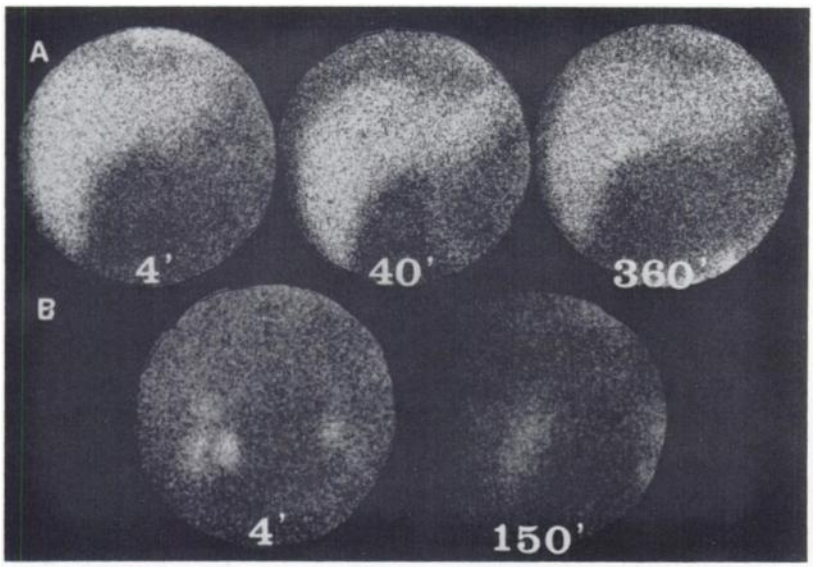

FIG. 2. (A) Hepatocellular disease, with decreased hepatic uptake, persistence of cardiac pool, delayed parenchymatous discharge, no stasis of tracer in bile ducts, gut activity at 40 min. (B) Severe hepatocellular disease: no hepatic uptake, persistence of kidney visualization.

and Fig. 4). In 28 of the 29 patients, gut activity was present; in 13 patients, all with bilirubin values below 10 mg/dl, the bile ducts were visualized but never with stasis of the tracer (Table 3).

In one patient with metastatic liver disease and a serum bilirubin of 9.8 mg/dl, a well-preserved uptake, without bile duct or gut visualization, led to a false inference of complete mechanical obstruction. In 34 of the 35 patients with hepatocellular disease, the scintigraphic criteria suggested that the jaundice was not related to any obstructive cause (Table 2).

Patients with obstructive jaundice. A normal or at least well-preserved hepatic uptake was observed in 51 patients, including the 40 patients with bilirubin below 10 mg/dl, and in 11 of the 16 patients with bilirubin above 10 mg/dl (Table 4).

Gut and bile ducts were visualized in 26 patients, all with bilirubin below 10 mg/dl (Table 4). In 23 of them, stasis of the tracer in the bile ducts was observed (Fig. 5). This latter finding was associated with a good hepatic uptake and gut activity, and thus indicated the existence of an incomplete mechanical obstruction (Table 2). However in the three remaining patients (two with cholangitis and one with cholecystitis), all with bilirubin below 10 mg/dl, there was no stasis of the tracer in the bile ducts. These findings, associated with well-preserved hepatic uptake, delayed hepatic discharge, and the presence of gut activity, led to three false-negative scintigraphic diagnoses (Table 2).

In 30 patients, gut and bile ducts were not visualized (Fig. 6). This group included the 16 patients with bilirubin above 10 mg/dl and 14 of the 40 patients with bilirubin below 10 mg/dl (Table 4). In 25 of these 30 patients, the association of well-preserved hepatic uptake, little if any discharge, and the absence of gut or bile-duct visualization, indicated complete mechanical obstruction

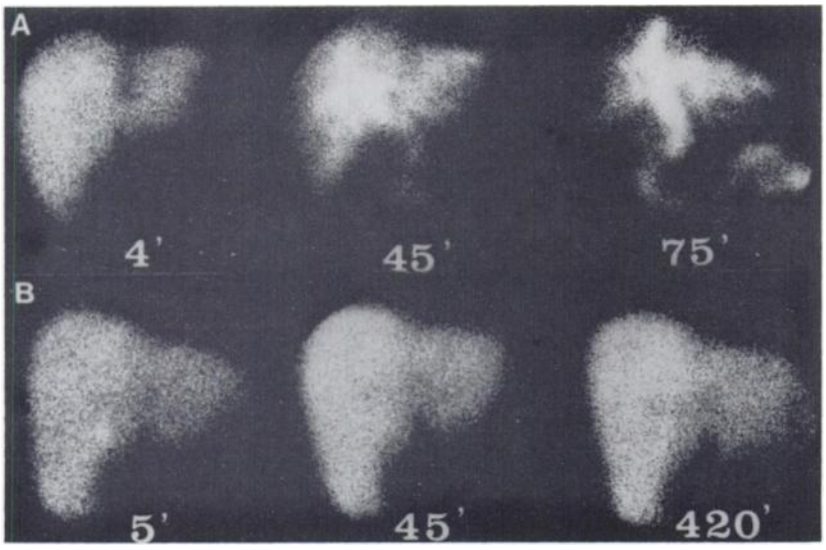

FIG. 3. Obstructive jaundice. (A) Incomplete mechanical obstruction: normal hepatic uptake, delayed parenchymatous discharge, stasis of tracer in bile ducts, gut activity. (B) Complete mechanical obstruction: well-preserved hepatic uptake, no parenchymatous discharge, no bile-duct or gut visualization.

TABLE 2. SUMMARY OF SCINTIGRAPHIC DATA FROM PATIENTS WITH HEPATOCELLULAR DISEASE OR OBSTRUCTIVE JAUNDICE

Final clinical diagnosis	No. of patients	Hepatic uptake 0–3*	Hepatic discharge 0–2†	Gut visualization 0–1‡	Bile-duct visualization 0–2‖	Scintigraphic conclusions
Hepatocellular disease						
	6	0	0	0	0	hepatocellular disease
	28	1–2	1	1	0–1	hepatocellular disease
	1	2	0	0	0	complete obstruction
Obstructive jaundice						
	23	2–3	1	1	2	incomplete obstruction
	3	2–3	1	1	0–1	hepatocellular disease
	25	2–3	0	0	0	complete obstruction
	5	0–1	0	0	0	hepatocellular disease

* Hepatic uptake: 0 = no uptake; 1 = very poor; 2 = decreased but well preserved; 3 = normal.
† Hepatic discharge: 0 = little if any discharge; 1 = delayed discharge; 2 = normal discharge.
‡ Gut visualization: 0 = nonvisualization; 1 = visualization.
‖ Bile-duct visualization: 0 = nonvisualization; 1 = normal; 2 = present, but with stasis.

(Table 2). In the five remaining patients (three with tumor of the pancreas and two with bile-duct carcinoma), all with bilirubin levels above 18 mg/dl, the liver was barely distinguishable, and this led to five false-negative scintigraphic conclusions (Table 2). In these five false-negative cases, the mean total serum bilirubin (24.8 ± 6.3 mg/dl, mean ± s.d.) was significantly higher ($p < 0.001$) than in the 25 patients with true-positive scans (9.5 ± 4.8 mg/dl). The duration of the jaundice was not significantly different. In one patient with pancreatic tumor and serum bilirubin of 8 mg/dl, a true-positive scan was obtained after 180 days of jaundice.

Accuracy of the Tc-diethyl-IDA scan in detection of obstructive jaundice. When the two groups of patients were taken together, the scintigraphic conclusions were correct in 82 of 91 patients, representing an overall accuracy of 90% (Table 5). However, the results of the radionuclide study were inversely related to the bilirubin levels. The overall accuracy dropped from 94% for bilirubin levels below 10 mg/dl to 67% for bilirubin above 20 mg/dl. True-positive scans were obtained in 37 of the 40 patients with obstructive jaundice and bilirubin below 10 mg/dl, whereas only one out of four scans appeared to be positive and correct in patients with obstructive jaundice and bilirubin above 20 mg/dl. The negative predictive value of the test was also influenced by the

TABLE 3. SCINTIGRAPHIC DATA IN RELATION TO SERUM BILIRUBIN VALUES IN 35 PATIENTS WITH HEPATOCELLULAR DISEASE

Scintigraphic data	Serum bilirubin <10 mg/dl	10–20 mg/dl	>20 mg/dl
Liver uptake			
none	0	3	3
very poor	2	4	2
decreased	21	0	0
normal	0	0	0
Gut			
not visualized	1	3	3
visualized	22	4	2
Bile-duct visualization			
none	10	7	5
normal	13	0	0
with stasis	0	0	0

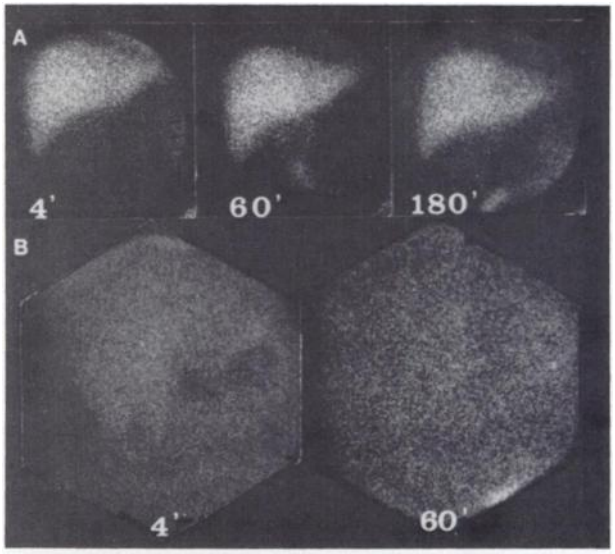

FIG. 4. Hepatocellular disease. (A) Hepatitis, serum bilirubin 4.2 mg/dl: well-preserved hepatic uptake, delayed parenchymatous discharge, no stasis of tracer in bile ducts, presence of gut activity. (B) Metastatic liver disease, serum bilirubin 23 mg/dl; no hepatic uptake.

TABLE 4. SCINTIGRAPHIC DATA IN RELATION TO SERUM BILIRUBIN VALUES IN 56 PATIENTS WITH OBSTRUCTIVE JAUNDICE

Scintigraphic data	Serum bilirubin <10 mg/dl	10–20 mg/dl	>20 mg/dl
Liver uptake			
none	0	1	1
very poor	0	1	2
decreased	17	8	1
normal	23	2	0
Gut			
not visualized	14	12	4
visualized	26	0	0
Bile duct visualization			
none	14	12	4
normal	3	0	0
with stasis	23	0	0

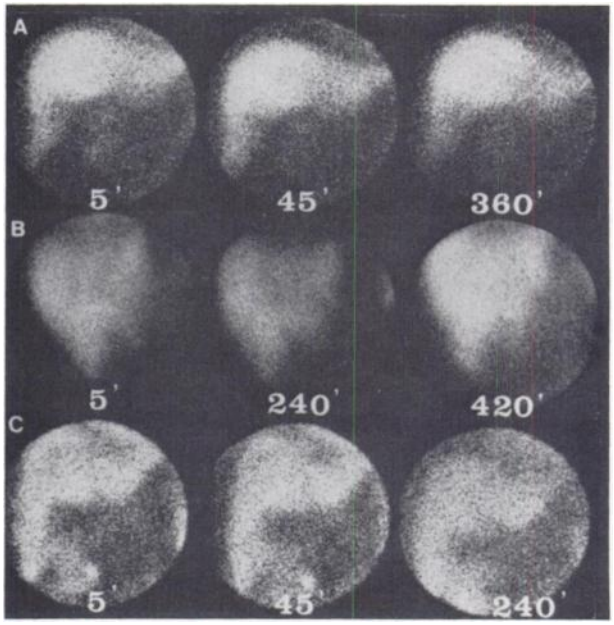

FIG. 6. Three patients with complete mechanical obstruction secondary to carcinoma of the pancreas, with well-preserved hepatic uptake and absence of bile-duct and gut visualization. (A) serum bilirubin 6.4 mg/dl. (B) Serum bilirubin 11.8 mg/dl. (C) Serum bilirubin 21 mg/dl.

degree of icterus, decreasing from 88% to 63% for bilirubin values respectively below 10 mg/dl and above 20 mg/dl. The positive predictive value, however, remained close to 100% even with bilirubin above 20 mg/dl.

DISCUSSION

In normal baboons, Wistow et al. (*3*) demonstrated that Tc-diethyl-IDA was a highly promising agent for imaging of the hepatobiliary system. Their findings were recently confirmed in an in vitro model as well as in patients with hepatobiliary disorders (*12–15*). Despite the superiority of diethyl-IDA over the other Tc-99m-labeled compounds, only preliminary reports have appeared on its value in the clinical evaluation of jaundiced patients (*5,7,16*).

In the present study, diethyl-IDA imaging allowed differentiation between hepatocellular and obstructive jaundice in 82 out of 91 patients, giving an overall accuracy of 90%. In the group of patients with hepatocellular disease, the scan allowed us to exclude an obstructive cause in all but one patient (97%). In patients with obstructive jaundice, however, the incidence of true-positive scans reached 86%. In our series, the score of 90% obtained with diethyl-IDA was distinctly better than the values reported with other Tc-99m-labeled compounds—e.g., 72.4% with pyridoxylidene glutamate (*17*), and 84% with the combination of dimethyl-IDA and *p*-butyl-IDA (*18*).

The duration of the jaundice did not influence the final issue of the scan, as illustrated by a true-positive scan obtained in one patient markedly jaundiced for 180 days.

Our results emphasized the inverse relationship between the serum bilirubin level and the reliability of the scan in detecting an obstructive jaundice. The overall accuracy decreased from 94% for bilirubin levels below 10 mg/dl, to 67% for bilirubin levels above 20 mg/dl, and the incidence of true-positive scans dropped from 93% to 25%. Five of the eight false-negative scans were obtained in patients with bilirubin levels above 18 mg/dl, and in each of these cases the liver was never clearly visualized. Stasis of the tracer in the bile ducts constituted a typical sign of obstructive jaundice. When the biliary tree and the gut were not visualized, however, the

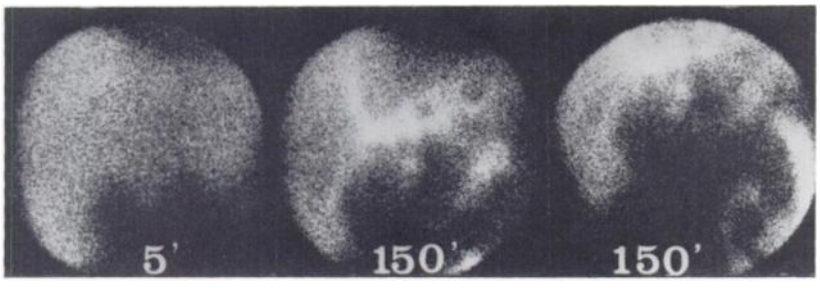

FIG. 5. Incomplete mechanical obstruction, secondary to choledocholithiasis, serum bilirubin 4.4 mg/dl; good hepatic uptake, stasis of tracer in bile ducts, but bowel activity present.

TABLE 5. PREDICTIVE VALUE OF Tc-DIETHYL-IDA SCINTIGRAPHY IN DETECTION OF OBSTRUCTIVE JAUNDICE

Serum bilirubin mg/dl	No. of patients	True positive (%)	True negative (%)	False positive (%)	False negative (%)	Positive predictive value (%)	Negative predictive value (%)	Overall accuracy (%)
<10	63	93	96	4	7	97	88	94
10–20	19	83	100	0	17	100	78	89
>20	9	25	100	0	75	100	63	67
Total	91	86	97	3	14	98	81	90

only criterion that helped to differentiate between mechanical obstruction and severe hepatocellular failure was the degree of the hepatic uptake. If the uptake remained well preserved, the jaundice was most likely of obstructive origin. In the present study, 93% of the patients with obstructive jaundice and bilirubin levels below 20 mg/dl presented at least a well-preserved hepatic uptake. Above 20 mg/dl of bilirubin, the hepatic uptake was very poor or nonexistent in 75% of patients with obstructive jaundice. It appears, therefore, that a bilirubin level close to 20 mg/dl sets the upper limit of reliability of Tc-diethyl-IDA in the detection of obstructive jaundice. The influence of the degree of the icterus on the reliability of the scan is not surprising, since bilirubin competitively inhibits the anionic clearance pathway of the Tc-IDA derivatives by the liver (*19,20*).

A very low false-positive incidence—and accordingly a high positive predictive value, even at high bilirubin levels—emphasized the usefulness of a positive scan in deciding whether the jaundice should be treated operatively or not. As long as the bilirubin did not exceed 10 mg/dl, even a negative scan remained reliable. Beyond this bilirubin level, however, the negative predictive value dropped from 88% to 78%, indicating that the diagnosis by scintigraphy was misleading in 22% of the negative scans.

In our hands, diethyl-IDA imaging has provided reliable information for the evaluation of a jaundiced patient, but it remains necessary to define the real clinical value of this method by comparisons with other noninvasive procedures, particularly ultrasonography. A clinical comparison of gamma and ultrasound imaging is currently in progress in our hospital. The preliminary data obtained in 41 jaundiced patients suggest that the overall accuracy of the two techniques in detecting an obstructive jaundice is similar, and that the incidence of true-positive results increases when both procedures are applied.

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