

Tc-99m Pyridoxylidene Glutamate in Jaundiced Patients

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Ninety patients, 85 of them jaundiced, were examined after the injection of Tc-99m pyridoxylidene glutamate, a substance rapidly concentrated by normal hepatocytes and excreted into the biliary tract. It appears in the gallbladder after 10–15 min, and in the gastrointestinal tract at 30 min. On the basis of the time of appearance in the intestine, four groups of patients were recognized: 1. Seventeen patients with a normal pattern, with visualization of the gut at 30 min. 2. Nineteen patients with a slight delay in passage, with appearance in the gut between 30–180 min. 3. Twenty-nine patients showing very slow excretion visualized only at 24 hr; 21 of these had parenchymatous disease of the liver, three choledocholithiasis and five had malignant disease causing partial obstruction. 4. Twenty-five patients with no visualization of the intestine; eight of them proved to be cases of medical jaundice, and 17 were surgical cases. Groups 3 and 4 comprise 54 patients where the question of medical or surgical jaundice was critical. If lack of intestinal activity is considered an indicating surgical jaundice, the accuracy of this study was only 72.4%.

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The problem of finding a reliable, noninvasive method to determine whether the cause of jaundice is intra- or extrahepatic, has constituted a challenge to nuclear medicine since the 1950s. In 1923 Dalprat (1) devised a test of liver function using rose bengal, which is removed from the bloodstream by the polygonal cells of the liver, secreted into the biliary ducts, concentrated in the gallbladder, and discharged into the duodenum. In 1955 Taplin et al. (2) reported the use of radioiodinated rose bengal in a liver uptake and excretion test performed with external monitoring. Nordyke and Blahd (3) followed the blood disappearance rate of the radiolabelled compound by sampling or monitoring, and found good correlation with the function of the polygonal cells. The liver-scanning techniques subsequently introduced served to add important anatomic information (4).

Burke and Halko (5) in 1966 introduced the use of the scintillation camera for continuous visualization of the dynamics of liver uptake and secretion. They were the first to suggest, on the basis of their results in a small number of cases, that [¹³¹I] rose bengal might be of value in diagnosing extrahepatic obstructive jaundice correctable by surgery. Follow-

ing this, other radioiodinated compounds such as toluidine blue (6) were tested for the same purpose.

The availability of Tc-99m stimulated a search for an alternative to previously used radioiodinated compounds, with the aim of obtaining higher-quality images of the biliary tract and an easier means of detecting very small amounts of labelled compounds excreted into the gut. Krishnamurthy et al. (7) developed Tc-99m penicillamine, which proved to have excellent concentration in the gallbladder in cases in which bilirubin was less than 2.5 mg%. Tc-99m dihydrothiocitric acid (8) showed a relatively late gallbladder concentration. Tc-99m mercaptoisobutyric acid (9) has shown rapid and almost total concentration in the liver, with good gallbladder visualization at 30 min and progressive secretion into the gut. Tc-99m tetracycline (10) shows early, high concentration in the kidneys, and thus is not ideal for liver or gallbladder studies.

In 1974 Baker et al. (11) first reported the re-

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TABLE 1. BOWEL VISUALIZATION TIME IN RELATION TO FINAL DIAGNOSIS

Group No.	Bowel visualization time	No. of patients	Normal	Medical jaundice	Surgical jaundice	
					Lithiasis	Tumor
1	15-30 min	17	5	5	7	
2	30-180 min	19	—	4	15	
3	24 hr	29		21	3	5
4	No visualization	25	—	8	2	15
Total		90	5	38	27	20

sults obtained with Tc-99m pyridoxylidene glutamate. This compound showed a high, rapid concentration in the polygonal cells, with a good visualization of the liver at 3-5 min and of the gallbladder 10 min after injection.

Following is the description of a clinical study carried out in 90 patients, 85 of them with jaundice, for the purpose of further determining the efficacy of this compound in the differential diagnosis of medical from surgical jaundice.

MATERIAL AND METHODS

A single-step kit preparation was developed using stoichiometric quantities of 0.26 mM pyridoxal HCl and sodium 1-glutamate together with 0.5 mM NaOH. These are placed in dried, unreacted form in an evacuated vial. Sterilization is then accomplished by gamma irradiation to 2.5 megarad. To attach the label, 4 ml of sterile ^{99m}TcO₄⁻ are added and the mixture autoclaved for 30 min at 120°C.

Animal tests with this compound showed rapid plasma clearance (t_{1/2} = 15 min), good liver uptake (22% at 5 min, 13% at 15 min), definite gallbladder visualization at 10-15 min, and high concentration in the gut (37% at 15 min). Kidney concentration was minimal at an early stage: 6% at 5 min, 4% at

15 min. No signs of toxicity were observed after mice had been injected with 500 doses.

Human studies were carried out in 90 patients, 85 of them with jaundice. All were followed up and a final diagnosis obtained by clinical evaluation, biopsy, surgery, or postmortem studies. In each patient 5 μ/kg of Tc-99m pyridoxylidene glutamate (Tc-PG) were injected intravenously. Injection was done under the scintillation camera and imaging of cardiac blood pool, liver, gallbladder, duodenum, and upper jejunum was obtained simultaneously. Imaging was done at 5-min intervals for the first 30 min and at 30-min intervals up to 3 hr, with a final image obtained at 24 hr. Two blood samples were taken, 5 and 20 min following injection, to determine the disappearance rate of Tc-99m from the plasma. The activities in these samples are used to assess the effectiveness of the radioagent in terms of R, the ratio (expressed as a percentage) of the blood activity at 20 min to that at 5 min.

RESULTS

As can be seen in Tables 1 and 2, four groups of patients emerged according to the time of appearance of the Tc-99m in the gastrointestinal tract:

1. Seventeen patients showed normal patterns (Fig. 1), with recognizable passage of the Tc-99m into the gastrointestinal tract within 30 min of injection. In this group, R averaged 57% and bilirubin 1.5 mg%.

2. Nineteen patients showed a delay in bowel visualization, which ranged from 30-180 min after injection. R averaged 66% and bilirubin 2.8 mg%. Most of these patients were suffering from lithiasis of the biliary tract; four patients had parenchymatous liver disease.

3. In 29 patients Tc-99m appeared in the bowel only in the 24-hr study (Fig. 2), with no visualization between injection time and 3 hr. Twenty-one of these patients suffered from parenchymatous liver disease, three had choledocholithiasis, and five had malignancies that apparently caused only partial obstruction. R averaged 70% and bilirubin 11 mg%.

TABLE 2. BOWEL VISUALIZATION TIME IN RELATION TO R (20'/5') BILIRUBIN, AND TRANSAMINASE VALUES

Bowel visualization time	R(20'/5') (%)	Bilirubin (mg%)	Transaminase
15-30 min	57 (50-65)	1.4 (0.8- 3)	53 (12-300)
30-180 min	66 (56-73)	2.8 (1.5- 6)	110 (16-225)
24 hr	70 (56-82)	11 (3 -29.8)	210 (72-320)
No visualization	73 (60-85)	12.2 (5.2-18.4)	225 (76-600)

* R = $\frac{\text{blood activity at 20 min}}{\text{blood activity at 5 min}}$

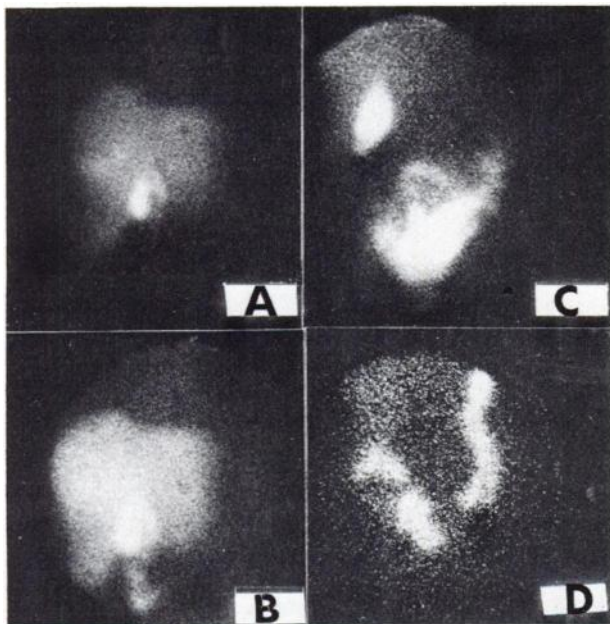


FIG. 1. Normal study. Good visualization of gallbladder at 10 min (A), with passage into duodenum-jejunum at 25 min. (B = 20 min, C = 30 min, D = 24 hr.)

4. This group of 25 patients was characterized by a complete lack of visualization of the gut, even in the 24-hr study. It included eight patients with severe parenchymatous liver disease (viral and toxic) and 17 surgical cases: 7 with pancreatic tumors, four with tumors of the bile ducts, four with metastatic disease of the liver and porta hepatis, and two with choledocholithiasis. R averaged 73% and bilirubin 12.2 mg%.

DISCUSSION

Pyridoxal is a member of the vitamin B₆ group involved in enzyme systems catalyzing transamination reactions (13). Condensation of the carboxyl group of pyridoxal and the amino group of glutamic acid may lead to Schiff base ligands. Most probably a Tc-99m chelate of the Schiff base is formed after reduction of the TcO₄ from a heptavalent to a tetravalent ion due to the reducing properties of the aldehyde group of the pyridoxal.

The qualities sought for a radiopharmaceutical destined to be used in the study of biliary flow are the following: high and rapid uptake by the polygonal cells, rapid secretion and concentration in the gallbladder, and rapid excretion into the duodenum. The timing and percentage distribution of the Tc-PG in animals and normal humans complies with our requirements. Thus, Tc-PG would appear to be ideal for the study of biliary flow. It must be realized, however, that in severely jaundiced patients there is considerable renal excretion of Tc-PG that may compli-

cate the interpretation of the study.

Ronai et al. (14) stated that, "The absence of gastrointestinal radioactivity at 18 hours after injection allowed a confident diagnosis of complete extrahepatic biliary obstruction to be made." In our study, however, of 25 patients in whom there was no radioactivity visualized in the gastrointestinal tract 24 hr after injection, eight were subsequently found to have severe parenchymatous disease while 17 proved to be cases of complete extrahepatic biliary obstruction, 15 of them due to malignancies. Thus, cases with very severe parenchymatous damage may show no evidence of Tc-PG flow into the bowel due both to the very low uptake and the pathologic changes that impair intrahepatic biliary circulation. Twenty-one percent of the 38 cases of parenchymatous liver disease in this series were found to be in this category.

In an attempt to obtain supplemental information to enhance the reliability of this procedure, we added a second parameter to that of imaging: an evaluation of the clearance efficiency of the polygonal cells as obtained by calculating the 20-min/5-min ratio (R). Prolonged obstruction results in severe cellular damage, with greatly impaired hepatocellular clearance capacity. In our series there was an overlapping of R values between medical and surgical jaundice in the two categories of severely jaundiced patients. However, there were no R values higher than 76% in patients with extrahepatic obstruction, whereas four patients with higher values had severe hepato-

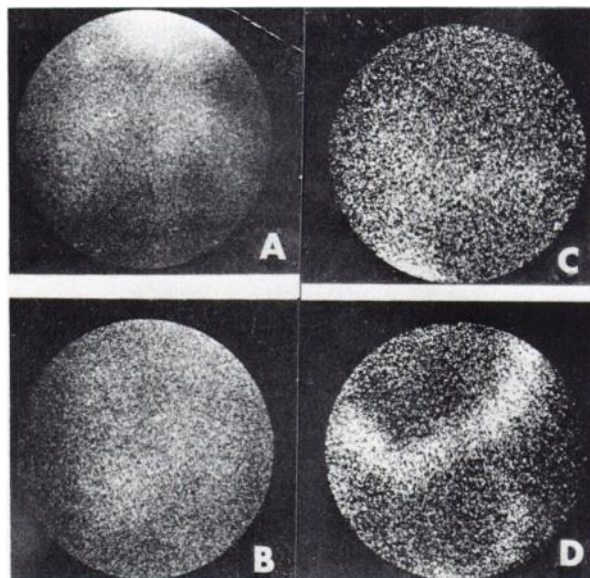


FIG. 2. Group 3 images made during the first 3 hr showed poor liver concentration, with no suggestion of delivery to gut. A = 5 min; B = 30 min; C = 180 min; D = 24 hr. (At 24 hr the colon is well defined.)

TABLE 3.

	Surgical jaundice	Medical jaundice
Nonvisualization	17	8
Visualization	8	25
Sensitivity = 68%.		
Specificity = 75%.		
Accuracy = 72.4%.		

cellular damage due to primary parenchymatous disease. This point deserves further investigation to evaluate its true diagnostic significance.

A second problem is the fact that among our surgical cases, five out of 20 tumors, and three out of five choledocolithiasis had partial obstruction with late visualization of bowel undifferentiable from the pattern in the medical jaundices. We analyzed the accuracy (Table 3) of the method assuming that we consider as surgical cases those that show lack of recognizable activity in the bowel 24 hr after injection. We found that 68% (sensitivity) of the surgical cases were completely obstructed and 75% (specificity) of the medical jaundices showed bowel visualization at 24 hr, while the rest were not recognizable from the surgical pattern. Thus the overall accuracy in our series is 72.4%.

CONCLUSION

Our approach to Tc-PG can be summed up as follows.

1. This radiopharmaceutical is excellent for obtaining clear visualization of the biliary system, even in cases in which bilirubin values are higher than 2-4 mg%, when cholecystography and cholangiopathy can provide no information.

2. The definite appearance of tracer in the small intestine less than 3 hr after injection (as seen in our first two groups) clearly establishes the patency of the common bile duct.

3. The late appearance of tracer at 24 hr can be seen in association with both parenchymatous lesions (73%) and incomplete obstruction (27%).

4. A complete lack of intestinal visualization was

due to extrahepatic obstruction in only 68% in our series of 25 patients showing this pattern.

5. The overall accuracy of the method in the detection of surgical jaundice was 72.4%.

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