

Hepatobiliary Scintigraphy: Morphine-Augmented Versus Delayed Imaging in Patients with Suspected Acute Cholecystitis

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CASE PRESENTATION

A 47-yr-old male was admitted to the hospital after he developed sharp, consistent, gnawing epigastric pain without radiation, as well as nausea and vomiting. The patient had a history of alcohol abuse, hypertension, cardiomyopathy, coronary artery disease, gastrointestinal bleeding, gout and anemia. The history of alcohol abuse dated back to at least 20 yr, with multiple admissions for pancreatitis. In the past, lipase and amylase levels were as high as 5000 U/liter (normal 0–200) and 400 U/liter (normal 0–140), respectively. An abdominal plain film showed calcifications within the pancreas. One week prior to admission, he had increased his alcohol intake and had consumed no other nutrients. One day prior to admission, he developed nausea and nonbilious vomiting.

The patient was a thin man in moderate distress, sitting hunched forward complaining of abdominal pain. His vital signs were normal and he was afebrile. On physical examination, there was marked tenderness in the epigastrium with guarding, but no rebound tenderness, and a negative Murphy's sign. Laboratory studies were within normal limits, including the amylase and lipase levels.

The presumptive diagnosis was alcohol-induced pancreatitis. However, the diagnosis of acute cholecystitis was also considered and a hepatobiliary scan was obtained. Images of the upper abdomen were acquired serially in the anterior projection after the intravenous administration of 3 mCi of ^{99m}Tc -diisopropyliminodiacetic acid (DISIDA). There was prompt and uniform uptake of radiotracer by the liver with excretion into the intrahepatic bile ducts, common bile duct, and small intestine.

The gallbladder was not visualized by 60 min postinjection of tracer (Fig. 1). Two milligrams of morphine sulfate with an additional 3-mCi dose of ^{99m}Tc -DISIDA was administered intravenously. Additional images were recorded for 30 min. The gallbladder was visualized at approximately 10–12 min postadministration of morphine, indicating a patent cystic duct (Fig. 2). Nonvisualization of the gallbladder prior to the administration of morphine was thought to be secondary to a prolonged fasting and/or chronic cholecystitis. An abdominal ultrasound and double contrast CT showed a gallbladder with a slight increase in thickness, multiple gallstones and calcifications of the pancreas.

The patient gradually improved with conservative therapy. On the third day, the patient was started on a clear liquid diet without any complications and was subsequently discharged with complete resolution of his abdominal pain.

DISCUSSION

Approximately 20% of patients who seek emergency medical attention for suspected biliary tract disease have acute cholecystitis. While the history, physical examination and laboratory findings are helpful in the differential diagnosis of acute cholecystitis, this disease must often be distinguished from other acute abdominal conditions. These include acute appendicitis, perforated or penetrating duodenal ulcer, acute or chronic gastric ulcer, acute pancreatitis and chronic cholecystitis (1).

Radiological studies such as roentgenograms of the abdomen are not particularly useful, if the clinical presentation is suggestive of acute cholecystitis, because the only information potentially available is the documentation of the presence of gallstones or air in the gallbladder and biliary tract. Ultrasonography shows gallstones, sludge or wall thickening, conditions that are associated but not specific for acute cholecystitis (2).

Cholescintigraphy has been considered to be the most accurate test in the evaluation of acute cholecystitis, with

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FIGURE 1. Images (2 min/frame) acquired from 30 min to 1 hr after i.v. administration of 3 mCi of ^{99m}Tc -DISIDA are shown. There was no visualization of the gallbladder up to 1 hr. The common bile duct and bowel are visualized.

a reported sensitivity and specificity of as high as 95% (3). However, delayed images up to 4 hr postinjection of radiotracer may be required to achieve this level of accuracy (2–5) because a variety of conditions, including insufficient fasting, prolonged fasting, chronic cholecystitis, acute pancreatitis, chronic alcoholism, common bile duct obstruction and hepatocellular dysfunction, can potentially cause delayed visualization of the gallbladder. This delay in achieving the correct diagnosis is a disadvantage, and in some clinical settings it may not be feasible to acquire delayed images. In addition, interpretation of delayed images may occasionally be difficult due to superimposed radiotracer activity from other structures such as colon.

Morphine contracts the sphincter of Oddi, which increases intraductal pressure and diverts bile flow into the gallbladder if the cystic duct is patent. The use of low-dose morphine appears to help avoid delayed imaging without any loss of the accuracy of the test (6–10).

Morphine-augmented Cholescintigraphy Versus Delayed Imaging:

At our institution, if the gallbladder does not visualize by 60 min following injection of ^{99m}Tc -DISIDA, provided radioactivity is identified in the small bowel, 2 mg of morphine sulfate are administered intravenously. Imaging is then continued for another 30 min. If the gallbladder does not visualize after morphine injection, a probable diagnosis of acute cholecystitis is made. We report here our prelimi-

nary data comparing the results of the morphine-augmented scintigraphy with those of delayed imaging.

Over a period of 10 mo, 157 patients were referred to our laboratory for cholescintigraphy for suspected acute cholecystitis.

Group 1. During the first 5 mo, 86 patients underwent cholescintigraphy. In 60 patients, the gallbladder was visualized within 1 hr. Medical records were reviewed. Three of these 60 patients had acute cholecystitis confirmed by surgery. The other 57 patients had a variety of abdominal or pelvic disorders.

In 26 patients, delayed images were obtained at different time points between 3 and 24 hr. Final diagnosis was made surgically in 19, and by physical and laboratory findings, other imaging studies and clinical course in the remaining 7 patients. Of the 26 patients who underwent delayed imaging, only 3 showed visualization of the gallbladder. None of these three patients had acute cholecystitis. Of the remaining 23 patients with nonvisualization of the gallbladder even on delayed views, only 8 had acute cholecystitis and the other 15 did not. These 15 false-positive studies included 11 with chronic cholecystitis, one with granulomatous cholecystitis, one with sclerosing cholangitis and two with other diseases.

Group 2. During the second 5-mo period, morphine-augmented cholescintigraphy was employed. Of the 71 studies performed during this period, the gallbladder was visualized within 1 hr in 50 patients. Only one patient had acute cholecystitis confirmed by surgery. The other 49 patients had other disorders comparable to those noted in Group 1.

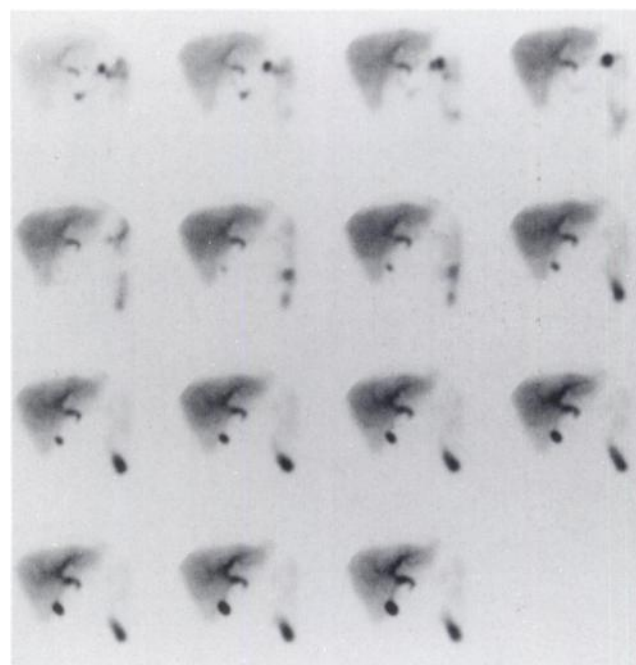


FIGURE 2. The second set of images were obtained immediately after i.v. injection of 2 mg of morphine followed by an additional administration of 3 mCi of ^{99m}Tc -DISIDA. The gallbladder was visualized after 12 min.

TABLE 1
Results of Conventional and Morphine-Augmented
Hepatobiliary Studies

Group	True-Positive	False-Negative	True-Negative	False-Positive	Total
1A	8	0	3	15	26
1	8	3	60	15	86
2A	8	1	9	3	21
2	8	2	58	3	71

The remaining 21 patients received 2 mg of morphine 60 min after tracer administration and imaging was continued for another 30 min. Final diagnosis was made surgically in 12 and by follow-up physical and laboratory findings, other imaging studies and clinical courses in 9 patients. In 10 patients, the gallbladder was visualized within 30 min following the injection of morphine. One of these patients was judged to have acute cholecystitis by follow-up physical and clinical course. Of the 11 patients whose gallbladder was not visualized after morphine injection, 8 had acute cholecystitis and 3 patients did not. Two of the three patients with false-positive studies had chronic cholecystitis, and one patient had cholangiocarcinoma with obstruction of the cystic duct.

Data Analysis. Of the patients (110) in Groups 1 and 2 with gallbladder visualization within 1 hr of ^{99m}Tc -DISIDA injection, four had acute cholecystitis. Therefore, the finding of gallbladder visualization within 1 hr had a negative predictive value of 96% (106/110).

In order to determine the efficacy of morphine-augmented scintigraphy versus delayed imaging, the patients were further subgrouped as follows (Tables 1 and 2):

- Group 1 (n = 86). All patients studied within the first 5 mo.
- Group 1A (n = 26). Patients who underwent delayed imaging.
- Group 2 (n = 71). All patients studied within the second 5 mo.
- Group 2A (n = 21). Patients who received morphine.

Overall accuracy of conventional cholescintigraphy with delayed imaging and morphine-augmented cholescintigraphy in Groups 1 and 2 (including the patients with

gallbladder visualization within 1 hr) was 79% and 93%, respectively. When the accuracy of cholescintigraphy in the Groups 1A and 2A (excluding the patients with gallbladder visualization within 1 hr) was determined for accurate comparison of the efficacy of delayed imaging versus morphine-augmented imaging, there was an even greater difference in the accuracy between the two approaches: 42% versus 81%, respectively.

Only 21 (13%) of 157 patients in our study had acute cholecystitis. When the proportion of the diseased population is low, specificity and positive predictive values become far more important indicators than sensitivity and negative predictive value in determining the efficacy of a given test. The specificity and positive predictive values of delayed imaging was only 17% and 35%, respectively, which is surprisingly low and unacceptable. The specificity and positive predictive value of morphine-augmented imaging was 75% and 73%, respectively, which is acceptable but somewhat lower than that reported in the literature. These poor results may be related in part to the composition of the patient population in our study which includes a fairly large number of patients with chronic cholecystitis. It may also be due in part to the small number of patients studied with morphine.

Chronic cholecystitis was the cause of almost all the false-positive studies for acute cholecystitis in our study. This is perhaps related to the presence of sludge occluding the cystic duct. In addition, prolonged fasting also can be a potential cause of delayed visualization due to stasis, especially in a sludge-filled gallbladder. Other reasons for delayed visualization of the gallbladder beyond 1 hr include insufficient fasting, acute pancreatitis, chronic alcoholism, common bile duct obstruction and hepatocellular dysfunction.

Some investigators recommend the routine administration of cholecystokinin (CCK) before a hepatobiliary study is performed in order to facilitate gallbladder filling in patients with chronic cholecystitis or in conditions of prolonged fasting (11). Others argue that the routine use of CCK markedly decreases the sensitivity of the study to detect chronic cholecystitis and do not recommend its routine use (12,13). Drane et al. have demonstrated that CCK injection prior to hepatobiliary scintigraphy was not useful in patients with severe illness, with or without hyperalimentation, or in patients with hepatocellular dysfunction (2). Kim et al. reported that CCK preadministration often causes delayed biliary-to-bowel transit of ^{99m}Tc -DISIDA (14), which can potentially be confused with partial common bile duct obstruction. The use of CCK is therefore questioned in this patient population. Besides, the gallbladder will visualize within 1 hr (70% in our series) in most patients. In contrast, morphine is only given to patients without gallbladder visualization.

Controversy also exists as to the usefulness of morphine in severely ill patients. Fig et al. reported that patients with severe intercurrent illness have a higher

TABLE 2
Statistical Analysis

Group	Sensitivity	Specificity	+PV	-PV	Accuracy
1A	100	17	35	100	42
1	70	80	35	95	79
2A	89	75	73	90	81
2	80	95	73	97	93

+PV = positive predictive value and
-PV = negative predictive value.

frequency of false-positive morphine-augmented cholescintigraphy (15). However, Flancbaum et al. found morphine of considerable help in a mixed population of 68 patients (sensitivity and specificity of 97 and 95%, respectively), including 25 patients who were critically ill and 26 with total parenteral nutrition (16).

While the physical and laboratory findings in the patient reported here suggested acute pancreatitis, acute cholecystitis was also considered because of detectable cholelithiasis on the imaging studies. Nonvisualization of the gallbladder 1 hr after the injection of ^{99m}Tc -DISIDA in this case could have been due to chronic cholecystitis, prolonged fasting and pancreatitis. Morphine-augmented cholescintigraphy was helpful in excluding acute cholecystitis in a relatively short period of time and obviated the need for an exploratory laparotomy in this severely ill patient.

Further studies are needed to determine the relative efficacy of CCK and morphine in the setting where acute cholecystitis is suspected. This comparison will be particularly important in patients with chronic cholecystitis to determine whether morphine-augmented cholescintigraphy has an acceptable accuracy compared with the preadministration of CCK and if it can be utilized as the method of choice in these patients.

Our results of conventional delayed imaging were rather disappointing. Our findings with morphine-augmented cholescintigraphy were somewhat poorer than those reported in the literature. Nevertheless, they were clearly superior to those of conventional delayed imaging.

REFERENCES

1. Dietrick NA, Caciopopo JC, Davis RP. The vanishing elective cholecystectomy. *Arch Surg* 1988;123:810.
2. Drane WE, Nelp WB, Rudd TG. The need for routine delayed radionuclide hepatobiliary imaging in patients with intercurrent disease. *Radiology* 1984;151:763.
3. Fink-Benett D, Freitas JE, Riply SD, Bree RL. The sensitivity of hepatobiliary imaging and real-time ultrasonography in the detection of acute cholecystitis. *Arch Surg* 1985;120:904-906.
4. Weissmann HS, Sugarman LE, Freeman LM. The clinical role of technetium-99m-Iminodiacetic acid cholescintigraphy. In: Freeman LM, Weissmann HS, eds. *Nuclear medicine annual 1981*. New York: Raven Press; 1981:35-90.
5. Freitas JE. Cholescintigraphy in acute and chronic cholecystitis. *Semin Nucl Med* 1982;12:18-26.
6. Choy D, Shi EC, McLean RG, Hoscho R, Murray IPC, Ham JM. Cholescintigraphy in acute cholecystitis: use of intravenous morphine. *Radiology* 1984;151:203-207.
7. Kim EE, Pjura G, Lowery P, Nguyen M, Pollac M. Morphine-augmented cholescintigraphy in the diagnosis of acute cholecystitis. *AJR* 1986;147:1177-1179.
8. Vazquez TE, Greenspan G, Evans DG, Halpern SE, Ashburn WL. Clinical efficacy of intravenous morphine administration in hepatobiliary imaging for acute cholecystitis. *Clin Nucl Med* 1988;13:4-6.
9. Keslar PJ, Turbner EH. Hepatobiliary imaging and the use of intravenous morphine. *Clin Nucl Med* 1987;12:592-596.
10. Fink-Benett D, Balon H, Robins T, Tsai D. Morphine-augmented cholescintigraphy: its efficacy in detecting acute cholecystitis. *J Nucl Med* 1991;32:1231-1233.
11. Eikman EA, Cameron JL, Colman M, Natarajan TK, Dugal P, Wagner HN Jr. A test for patency of the cystic duct in acute cholecystitis. *Ann Intern Med* 1975;82:318-322.
12. Freeman LM, Sugarman LA, Weissmann HS. Role of cholecystokinetic agents in Tc-99m-IDA cholescintigraphy. *Semin Nucl Med* 1981;11:186-193.
13. Fink-Benett D. The role of cholecystogues in the evaluation of biliary tract disorders. In: Freeman LM, Weissmann HS, eds. *Nuclear medicine annual 1985*. New York: Raven Press; 1985:107-132.
14. Kim CK, Palestro CJ, Solomon RW, Molinari DS, Lee SO, Goldsmith SJ. Delayed biliary-to-bowel transit in cholescintigraphy after cholecystokinin treatment. *Radiology* 1990;176:553-556.
15. Fig LM, Wahl RL, Stewart RE, Shapiro B. Morphine-augmented hepatobiliary scintigraphy in the severely ill: caution is in order. *Radiology* 1990;175:467-473.
16. Flancbaum L, Alden SM. Morphine cholescintigraphy. *Surg Gynecol Obstet* 1990;171:227-232.