Morphine-Augmented Cholescintigraphy: Its Efficacy in Detecting Acute Cholecystitis

D. Fink-Bennett, H. Balon, T. Robbins, and D. Tsai

Department of Nuclear Medicine and Department of Pathology, William Beaumont Hospital, Royal Oak, Michigan

Cholescintigrams were performed in 158 patients suspected of having acute cholecystitis after administration of 185 Mbq (5 mCi) of ^{99m}Tc-mebrofenin or disofenin. Morphine sulfate, 0.04 mg/kg was given intravenously if there was nonvisualization of the gallbladder at 40–60 min provided that radiotracer was seen within the small bowel. Acute cholecystitis was deemed present if there was nonvisualization of the gallbladder 30 min post-morphine administration; no cystic duct obstruction was present if the gallbladder was demonstrated pre- or post-morphine administration. A final diagnosis was estimated in 51 postoperative patients histologically, the remainder having their final diagnosis gleaned from their medical records. The sensitivity, specificity, positive and negative predictive value of morphine-augmented cholescintigraphy in detecting acute cholecystitis was 94.6, 99.1, 97.2, and 98.3%, respectively. These findings indicate that morphine-augmented cholescintigraphy detects acute cholecystitis with as high a degree of accuracy as conventional hepatobiliary scintigraphy, yet requires only 1.5 hr to establish the diagnosis.

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The sensitivity and specificity of hepatobiliary scintigraphy in confirming the clinical impression of acute cholecystitis is greater than 95% (*1*). To achieve this degree of reliability, however, images must be obtained up to 4 hr post-radiotracer administration. If imaging is ceased after 1 hr, the sensitivity and specificity of the procedure is reduced to 80%–88% (*2–4*). This occurs as individuals with increased intraluminal gallbladder pressure from highly viscous stagnant bile require more time for enough radiotracer to enter the gallbladder to permit its visualization (*3,4*).

To determine if morphine-augmented cholescintigraphy is as accurate as conventional hepatobiliary scintigraphy in detecting acute cholecystitis, we retrospectively analyzed the results of 158 cholescintigrams performed on patients in whom a diagnosis of acute cholecystitis was clinically suspected (*5–8*).

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For reprints contact: Darlene Fink-Bennett, MD, William Beaumont Hospital, 3601 W. 13 Mile Rd., Royal Oak, MI 48073.

MATERIALS AND METHODS

We retrospectively analyzed the results of 158 cholescintigrams performed on 58 males (15–90 yr) and 100 females (18–89 yr) in whom acute cholecystitis was clinically suspected. All scintigrams were performed in the Department of Nuclear Medicine from October 1987 to August 1988.

Hepatobiliary scans were performed after a minimum 2-hr fast and following the intravenous administration of 185 MBq (5 mCi) of ^{99m}Tc-disofenin or ^{99m}Tc-mebrofenin. Patients who had fasted for greater than 48 hr were given 0.02 μg/kg cholecystokinin (CCK) 30 min prior to the intravenous administration of the radiotracer. An anterior, 1,000,000 count, standard gamma camera image of the liver and biliary tree was obtained at 5 min. Images were then obtained at 10-min intervals for a set time, determined from the number of seconds required to obtain the initial anterior 1,000,000 count biliary image. Lateral views were obtained at 30 and 60 min post-radiotracer administration. Morphine sulfate, 0.04 mg/kg diluted in 10 ml of saline was administered intravenously over a 3-min duration if there was nonvisualization of the gallbladder at 40–60 min and if radiotracer was seen in the small bowel. Five-minute serial post-morphine images were then obtained for 30 min for the same time as the pre-morphine images.

Acute cholecystitis was scintigraphically deemed present if there was persistent nonvisualization of the gallbladder 30 min post-morphine administration; no cystic duct obstruction was present if the gallbladder visualized 5–30 min post-morphine administration.

A common duct occlusion was considered if there was persistent nonvisualization of the biliary tree and small bowel for at least 6 hr.

Morphine was not used if contraindicated (i.e., the patient had a known allergy to it or codeine, had pancreatitis, or was a known narcotics addict).

Acute cholecystitis was deemed present only when it was confirmed pathologically by the identification of either hemorrhagic necrosis of the gallbladder wall, moderate to marked acute inflammation, marked mural edema, mucosal ulceration, or fibrin deposition.

RESULTS

Of the 158 patients clinically suspected of having acute cholecystitis, 61 required morphine augmentation to determine if their cystic duct was patent. Five patients demonstrated findings indicative of common bile duct obstruction (indeterminate pattern of acute cholecystitis) and were therefore excluded from analysis.

TABLE 1
Results of Morphine Augmentation

	No. patients	True-Positive		True-Negative		False-Positive		False-Negative	
		Path Dx	Med Dx	Path Dx	Med Dx	Path Dx	Med Dx	Path Dx	Med Dx
Morphine-Augmented	61	30	5	4	19	1	0	2	0
Non-Morphine-Augmented	92	0	0	14	78	0	0	0	0

Of the 61 patients requiring morphine augmentation, 37 underwent a cholecystectomy and 24 were medically managed. Of the surgically confirmed cases, there were 30 true-positive, 4 true-negative, 1 false-positive, and 2 false-negative hepatobiliary scans. Of the medically treated patients, 5 had true-positive and 19 had true-negative biliary scans. None of the 92 patients whose gallbladder visualized within 60 min post-radiotracer administration had acute cholecystitis. Fourteen of these patients underwent a cholecystectomy. None had acute cholecystitis (Table 1).

DISCUSSION

The sensitivity, specificity, positive and negative predictive value of morphine-augmented cholescintigraphy for detecting acute cholecystitis were 94.6, 99.1, 97.2, and 93.3%, respectively. These findings indicate that morphine-augmented cholescintigraphy detected acute cholecystitis with as high a degree of accuracy as conventional hepatobiliary scintigraphy, yet required only 1.5 hr to establish the diagnosis (*1,4*). Care, however, must be taken when performing and interpreting morphine-augmented cholescintiscans, as is true with conventional hepatobiliary scintigraphy, to prevent false-positive and false-negative studies from occurring. In one of our patients, ^{99m}Tc-IDA biliary to bowel transit was so rapid that insufficient quantities of radiotracer remained in the hepatocytes to permit visualization of the gallbladder post-morphine augmentation despite a patent cystic duct, thereby creating a false-positive study. In situations such as this, where only residual amounts of radiotracer remain, one can reinject (booster) the patient and then morphine augment earlier at approximately 20–30 min. If there is then persistent nonvisualization of the gallbladder 30 min post-morphine augmentation, a cystic duct obstruction can be diagnosed accurately.

Another patient demonstrated a "dilated cystic duct sign" (radiotracer located within a patent cystic duct proximal to its site of obstruction) and following morphine augmentation demonstrated radiotracer within the gallbladder itself. The increased pressure created within the common bile duct and intrahepatic biliary tree may have dislodged the cystic duct stone creating a false-negative morphine-augmented hepatobiliary scan. When a dilated cystic duct sign is present, it is probably prudent not to augment with morphine, but to obtain delayed hepatobiliary images to confirm that the focus of increased accumulation of radiotracer adjacent to the common bile duct is truly a manifestation of an obstructed duct (i.e., acute cholecystitis) (*9*). A second false-negative morphine-augmented cholescintiscan occurred in a patient with acute acalculous cholecystitis. In this patient, the increased intraluminal pressure within the cystic duct and gallbladder created by the acutely inflamed cystic duct and gallbladder wall were not sufficient to prevent radiotracer from entering either of them post-morphine augmentation. In situations such as these, as in conventional hepatobiliary scintigraphy, where there is a high clinical index of suspicion for acute acalculous cholecystitis and potential for a false-negative hepatobiliary scan, real time ultrasonography, computed tomography, and indium-white blood cell scintigraphy should be employed in an attempt to prevent a misdiagnosis. Fortunately, acalculous acute cholecystitis accounts for only 5%–6% of all patients with an acute hemorrhagic gallbladder wall and, thus, does not account for a large portion of the population evaluated for the presence of a cystic duct obstruction and acute cholecystitis (*10–13*).

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EDITORIAL

Is Morphine Injection Useful in the Scintigraphic Diagnosis of Acute Cholecystitis?

Cholescystectomy is the most common major surgical procedure performed in the United States and approximately 500,000 cholecystectomies are performed each year (*1*). With new techniques such as laparoscopic or ambulatory cholecystectomy, the number of surgical treatments for acute cholecystitis is anticipated to increase.

Biliary colic, acute cholecystitis, and chronic cholecystitis represent the spectrum of gallbladder disease. Acute cholecystitis refers to acute inflammation of the gallbladder due to generally complete obstruction of the cystic duct by an impacted stone or one attempting to pass from the gallbladder through the cystic duct and into the common duct. Acalculous cholecystitis accounts for about 5% of acute cholecystitis and is found in patients with overwhelming sepsis, prolonged starvation, cystic artery occlusion, and prolonged hyperalimentation (*2*).

Although the clinical presentation of acute cholecystitis has been well described, the symptoms can be mimicked by various pathologic conditions. The diagnosis of acute cholecystitis is particularly difficult to establish in critically ill patients. Therefore, surgeons have come to rely on imaging results to confirm or disprove clinical suspicions (*3*). Ultrasound provides information about gallbladder anatomy and shows the presence of stones with relatively high accuracy. Cholescintigraphy with ^{99m}Tc-imminodiacetic compounds is a functional test of the gallbladder and assesses the patency of the cystic duct. The persistent nonvisualization of the gallbladder in the presence of normal excretion into the small intestine is highly suggestive of acute cholecystitis in the symptomatic patient. Chronic cholecystitis is suggested when symptoms have abated and the gallbladder does not visualize. However, failure of the gallbladder to fill can be attributed not only to the obstruction of the cystic duct but also to prolonged fasting, total parenteral nutrition, pancreatitis, hepatocellular disease, alcoholism, and critical illness (*4*). False-positive cholescintigraphy has been reported in more than one-third of the critically ill patients with suspected acute cholecystitis (*3*). The mechanism for nonfilling of the gallbladder in these patients is unclear, but it may be related to altered biliary dynamics and water resorption.

In this issue of *The Journal of Nuclear Medicine*, Fink-Bennett et al. (*5*) report that morphine-augmented cholescintigraphy in 61 patients detects acute cholecystitis with a high degree of accuracy similar to conventional cholescintigraphy, yet only 1.5 hr was required to establish the diagnosis. This confirms the previous reports on the utility of morphine injection in the diagnosis of acute cholecystitis (*6,7*). Recently, Flancbaum and Alden (*8*) also reported that the use of morphine improved the diagnostic accuracy of cholescintigraphy in 68 patients, including 25 critically ill patients, from 43% to 96% and also reduced the false-positive rate from 87% to 5%. These reports include rare instances of false-negative cholescintigraphy anticipated in certain patients with acalculous cholecystitis.

Injection of morphine sulfate (0.04 mg/kg) may produce up to a ten-fold increase in resting common bile duct pressure with the contraction of the sphincter of Oddi (*6*) and thus dislodge a stone from the cystic duct by the increase in pressure resulting in flow of radiotracer into the gallbladder. Fink-Bennett et al. (*5*) demonstrated a "dilated cystic duct sign" (radiotracer within a cystic duct proximal to the obstruction site) and suggested that it is probably prudent not to augment with morphine but to obtain delayed images when a dilated cystic duct sign is present.

The false-positive rate is controversial. Fink-Bennett et al. (*5*) and Flancbaum and Alden (*8*) reported that it is low, although Fig et al. (*9*) have recently shown a rate as high as 60% in a group of seriously ill patients. Rapid biliary to bowel transit of the radiotracer or insufficient quantity of the radiotracer remaining in the hepatocytes seems to be responsible for the false-positive studies. Stasis of the gallbladder with water reabsorption from the

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For reprints contact: E. Edmund Kim, MD, Department of Nuclear Medicine, University of Texas M.D. Anderson Cancer Center, 1515 Holcombe Blvd., Houston, TX 77030.