Morphine Augmentation Increases Gallbladder Visualization in Patients Pretreated with Cholecystokinin

Charles C. Chen, Lawrence E. Holder, Christophe Maunoury and Cinthia I. Drachenberg
Departments of Diagnostic Radiology and Pathology, Division of Nuclear Medicine, University of Maryland Medical System, Baltimore, Maryland

The purpose of this study was to determine if a combination of cholecystokinin (CCK) pretreatment followed by morphine augmentation improved the detection of cystic duct patency compared with CCK pretreatment only. **Methods:** One hundred fifty-five patients with suspected acute cholecystitis had scintigraphy performed with 185–481 MBq (5–13 mCi) ^{99m}Tc-mebrofenin adjusted to the patients' total bilirubin levels. All patients were pretreated with 0.02 μg/kg sincalide injected intravenously over 3–5 min. Sequential imaging was performed until gallbladder activity was identified or up to 90 min postinjection of mebrofenin. If no gallbladder was identified, a second dose of mebrofenin was given as necessary to have tracer in the biliary system. Then, 0.04 mg/kg intravenous morphine sulfate was administered, followed by imaging for up to 30 min or until gallbladder visualization. **Results:** Twenty-eight percent (43/155) of the patients pretreated with CCK had nonvisualization of the gallbladder at 90 min postinjection of radiotracer. After intravenous morphine, the gallbladder was identified in 42% (18/43) of these patients ($p = 0.0001$). **Conclusion:** Hepatobiliary imaging with CCK pretreatment and imaging for 90 min was insufficient to identify all patent cystic ducts. Morphine augmentation significantly increased the frequency of gallbladder visualization in patients pretreated with CCK.

Key Words: cholecystitis; cholecystokinin; morphine-augmented cholescintigraphy

J Nucl Med 1997; 38:644–647

Pretreating all patients clinically suspected of having acute cholecystitis with cholecystokinin (CCK) as a routine part of hepatobiliary imaging protocols has been proposed to reduce imaging time from 4 hr to 90 min (*1*). The role of CCK before cholescintigraphy is to evacuate the gallbladder and optimize subsequent gallbladder filling with radiotracers (*1–3*).

Morphine augmented cholescintigraphy also has been used to decrease imaging time. Morphine causes contraction of the sphincter of Oddi. This increases intraductal pressure and forces the bile from the common bile duct into the gallbladder, if the cystic duct is patent. Some authors have suggested that morphine be injected when the gallbladder has not been visualized at 60 min postinjection of radiotracer. Total imaging time in these protocols was also reduced from 4 hr to 90 min (*1,4,5*).

This was a prospective study to evaluate whether 90 min of imaging after CCK pretreatment was sufficient to identify all patent cystic ducts and determine if a combination of CCK pretreatment followed by morphine augmentation improved the detection of cystic duct patency compared with CCK pretreatment only.

Received Mar. 5, 1996; revision accepted Jul. 22,1996.

For correspondence or reprints contact: Charles C. Chen, MD, Peoria Radiology, St. Francis Medical Center, 530 North East Glenn Oak Ave., Peoria, IL 61637.

MATERIALS AND METHODS

Patients

Hepatobiliary scans were performed in 174 consecutive patients at the University of Maryland Medical System from September 1993 to February 1995. The patients were studied because of clinical suspicion for acute cholecystitis.

Excluded from analysis were 19 patients who failed to complete the study protocol. These patients either had imaging performed for less than 90 min or did not receive morphine for the following reasons: eight patients with decreased biliary excretion due to severe hepatocellular disease or cholestasis, four patients with severe abdominal pain sent to surgery urgently, two unstable patients with hypotension, one patient with previous sphincterotomy, one patient with choledochojejunostomy, two patients with small bowel activity misinterpreted as gallbladder activity and one patient with a rim sign and acute gangrenous cholecystitis. The final sample consisted of 155 patients (Table 1).

Imaging Protocol

All patients were premedicated with 0.02 μg/kg of sincalide (Kinevac), a synthetically prepared C-terminal octapeptide of cholecystokinin. Sincalide was injected intravenously over 3–5 min to reduce adverse reactions and to prevent spasm at the neck of the gallbladder. The latter can occur if sincalide is given as a bolus injection (*1*).

Fifteen to 40 min later (mean 20 min), 185–481 MBq (5–13 mCi) ^{99m}Tc-mebrofenin were administered. The dose of mebrofenin was adjusted to the total bilirubin level of the patient: 185 MBq (5 mCi) if the total bilirubin was ≤1 mg/dl, 185–370 MBq (5–10 mCi) if the total bilirubin was 1–15 mg/dl and 370–555 MBq (10–15 mCi) if the total bilirubin was ≥15 mg/dl. Most of the patients received 185–222 MBq (5–6 mCi).

Sequential planar images were then obtained until the gallbladder was visualized or up to 90 min postinjection of mebrofenin. If the gallbladder was not identified at 90 min, 0.04 mg/kg of morphine was injected intravenously. If most of the activity was in the small bowel and little activity remained in the liver and bile ducts, a second dose equal to the first dose of mebrofenin was injected approximately 5 min before administration of morphine to refill the bile ducts. Additional sequential planar images were obtained until the gallbladder was identified or up to 30 min postinjection of morphine.

Pathological Diagnosis

Hematoxylin and eosin stained sections from the body and neck of each gallbladder were examined by a pathologist blinded to the results of scintigraphy. Presence or absence of gallstones was determined on gross pathology.

The strict pathological criteria for acute cholecystitis was if one or more of the following was found: transmural neutrophilic infiltration, gangrenous necrosis, mucosal ulcerations associated

TABLE 1
Patient Data

Number of patients	155
Age (yr)	45 ± 17 (range 14–86)
Gender	79 women, 76 men
Abdominal pain	76% (118/155)
Right upper quadrant pain	52% (81/155)
Total bilirubin	1.7 ± 2.1 mg/dl (range 0.1–11.2)
Alkaline phosphatase	167 ± 133 IU/liter (range 32–743)
SGOT	98 ± 156 IU/liter (range 6–862)
SGPT	93 ± 176 (range 7–994)
Hours fasting	42 ± 62 (range 3.5–336)

with microabscesses or massive transmural edema associated with scattered neutrophilic infiltrates and acute serositis. The liberal criteria for acute cholecystitis was if subintimal neutrophilic infiltration or gallbladder wall edema was found.

Additionally, chronic cholecystitis was diagnosed if one or more of the following was found: subepithelial aggregates of lymphocytes or plasma cells, scattered lymphoid aggregates throughout the wall, granulomatous chronic inflammation of the submucosa associated with bile pigment or stones or inflammatory proliferation of the mucosa with fusion of the mucosal folds (cholecystitis glandularis).

Statistical Analysis

Patient demographic data were compared with chi-squared and analysis of variance (ANOVA) tests for discrete and continuous variables, respectively. P values < 0.05 were considered significant.

RESULTS

Gallbladder Visualization

All patients were pretreated with CCK. The gallbladder was visualized within 90 min in 72% (112/155), within 60 min in 71% and within 30 min in 61% of the patients. The gallbladder was not visualized at 90 min postinjection of radiotracer in 28% (43/155) of the patients. Morphine was administered to these patients, and the gallbladder was identified in 42% (18/43). Gallbladder visualization with the combination of CCK pretreatment followed by morphine augmentation was significantly higher than with CCK pretreatment only ($p = 0.0001$, Table 2).

Cohort Without Histopathology

Seventy-two percent (112/155) of the patients did not have a cholecystectomy after cholescintigraphy. With CCK pretreatment only, 21% (24/112) of the gallbladders were not visualized after 90 min of imaging. With morphine, 16 additional gallbladders were visualized. This significantly ($p < 0.005$) decreased the gallbladder nonvisualization rate to 7% (8/112).

The eight patients with gallbladder nonvisualization may have had acute cholecystitis but were managed conservatively, so no histopathological proof was available. Two of these patients were treated with ultrasound guided percutaneous gallbladder drainage and antibiotics. One patient died from disseminated aspergillosis as a complication of acute myelogenous leukemia. The remaining five patients with gallbladder nonvisualization were treated with antibiotics.

TABLE 2
Gallbladder Visualization in Patients with CCK Pretreatment Before and After Morphine Augmentation

	CCK only*	CCK and morphine*	Total
GB not visualized	43	25	68
GB visualized	0	18	18
Total	43	43	86

*$p = 0.0001$, chi-square was 20.3 with Yates correction, 22.8 without Yates correction.
GB = gallbladder.

Analysis Using Strict Criteria for Acute Cholecystitis

Histopathological confirmation from cholecystectomies was available in 28% (43/155) of the patients. None of the resected gallbladders was normal. Acute cholecystitis using strict criteria was found in 30% (13/43), chronic cholecystitis in 91% (39/43) and 21% (9/43) had both acute and chronic cholecystitis. Gallstones were found in 65% (28/43) of the gallbladders on gross pathological examination.

With CCK pretreatment only, 44% (19/43) of the gallbladders were not visualized after 90 min of imaging (Table 3). With the additional use of morphine, two additional gallbladders were visualized and only chronic cholecystitis was found on histopathology when strict criteria were used. This decreased the gallbladder nonvisualization rate to 40% (17/43).

There were eight false-positive studies using strict criteria for acute cholecystitis (Table 3), i.e., gallbladder nonvisualization after the combination of CCK followed by morphine administration in patients found to have only chronic cholecystitis on histopathology. None of the resected gallbladders were normal. Three patients had surgery delayed 32, 48 and 78 days after cholescintigraphy; one patient had a 1.2 cm gallstone within the gallbladder, one patient had a gallbladder filled with mucoid sludge, and three of the gallbladders were filled with multiple, small gallstones.

Of the four false-negative studies (Table 3), i.e., gallbladder visualization in patients with histopathologic acute cholecystitis, three were in patients with diabetes mellitus and end-stage renal disease. One of these patients had a renal transplant, and the gallbladder was visualized within 15 min, while the other two were hemodialysis dependent and had gallbladders that visualized within 45 min. All three patients had abdominal CT scans or ultrasound studies within one day of cholescintigraphy that showed sludge-filled gallbladders without evidence for acute cholecystitis. The fourth patient had a heart transplant 3 mo prior and was receiving immunosuppressive therapy (cyclosporine and azathioprine), and correlative ultrasound showed a large, sludge-filled gallbladder with only mild gallbladder wall thickening.

Analysis Using Liberal Criteria for Acute Cholecystitis

When pathological examination of the resected gallbladders was repeated using liberal criteria (Table 3), the prevalence of acute cholecystitis increased from 30% using strict criteria to 56% using liberal criteria. As a consequence of using more liberal criteria, nine of the previous 10 false-positive studies using CCK pretreatment only and strict criteria for acute cholecystitis were converted to true positives, the positive predictive value increased from 47% to 95%, and the specificity of cholescintigraphy increased from 69% to 95%. After the additional use of morphine, the remaining one false-positive study was converted to a true negative and the specificity increased from 95% to 100% while the sensitivity of cholescintigraphy for detecting acute cholecystitis decreased from 75% to 71%.

DISCUSSION

Pretreating all patients suspected of having acute cholecystitis with CCK and imaging for only 90 min has been suggested (*1*) after Eikman et al. (*2*) reported that 90 min of imaging in

TABLE 3
Scan Results in Patients with Surgical Confirmation

AC criteria	Augmentation	Scan results	AC	Not AC	Sens	Spec	PPV	NPV	AC Prev
Strict	CCK only	19 GB nonvis	9	10	69%	67%	47%	83%	30%
		24 GB vis	4	20					
	CCK and morphine	17 GB nonvis	9	8	69%	73%	53%	85%	30%
		26 GB vis	4	22					
Liberal	CCK only	19 GB nonvis	18	1	75%	95%	95%	75%	56%
		24 GB vis	6	18					
	CCK and morphine	17 GB nonvis	17	0	71%	100%	100%	73%	56%
		26 GB vis	7	19					

Sens = sensitivity; Spec = specificity; PPV = positive predictive value; NPV = negative predictive value; AC = acute cholecystitis; Prev = prevalence; GB = gallbladder; nonvis = nonvisualization; vis = visualization.

patients treated with CCK was sufficient to identify cystic duct patency. The results of our study indicated that pretreating all patients with CCK and imaging for only 90 min was insufficient to identify all patients with patent cystic ducts. A significant number of gallbladders were visualized after the additional administration of morphine. This increased the positive predictive value and specificity of cholescintigraphy.

Initial analysis with strict criteria for acute cholecystitis in our study group suggested lower positive predictive values and specificities than reported in other studies. However, when liberal criteria for acute cholecystitis were used, our protocol of CCK pretreatment followed by morphine augmentation produced results that were similar those of studies reported in a recent review of delayed imaging and morphine augmentation studies (*4*). It has been shown that as pathological criteria for acute cholecystitis varied from strict to liberal, the sensitivity of cholescintigraphy decreased, and the specificity increased (*6*). In our group of patients, both the sensitivity and specificity increased as pathological criteria for acute cholecystitis changed from strict to liberal, and the prevalence rate of acute cholecystitis increased from 30% to 56% (Table 3).

Strict criteria for acute cholecystitis required more severe transmural inflammatory changes but ignores the natural history of repeated bouts of cholecystitis that cause fibrosis and prevents subsequent inflammatory changes from becoming transmural (*6*). In contrast, the scintigraphic finding of cystic duct obstruction is more sensitive to early inflammatory changes. Thus, it was not surprising that cystic duct obstruction was more closely related to acute cholecystitis as defined by liberal criteria.

Using liberal criteria for the diagnosis of acute cholecystitis, the specificity of 95% after CCK pretreatment was comparable to the 88% to 100%, but the sensitivity of 75% was lower than the 95% to 100% reported in hepatobiliary studies using delayed imaging or morphine augmentation (*4*). The additional use of morphine in combination with CCK pretreatment further increased specificity and decreased sensitivity (Table 3).

Whether the lower sensitivity for detecting acute cholecystitis was related to pharmacologic intervention or due to patient selection biases is uncertain and requires further study. Cholescintigraphy in patients with severe intercurrent illness has been shown to be both less sensitive and less specific (*7*).

There are also unresolved issues regarding the optimal protocol for CCK administration that may have affected the results of this study. Gallbladder emptying and filling in normal patients can be quite variable depending on the dose and timing of CCK injections (*8–10*). In addition, an atonic gallbladder with or without a patent cystic duct may not respond to CCK (*1,3*). CCK administered as 0.02 μg/kg over 3–5 min in this study was comparable to other studies. Fink-Bennett et al. (*1*) used 0.02 μg/kg injected over 3 min and Swayne et al. (*11*) used 0.02 μg/min over 5 min. Krishnamurthy and Krishnamurthy (*9*) have suggested that 0.01 μg/kg infused over 3 min (3.3 ng/kg/min) is the optimal physiologic dose, and higher doses may not induce gallbladder emptying in healthy volunteers. Ziessman et al. (*10*) showed that doses of 0.02 μg/kg or 0.01 μg/kg infused over 30 min (0.67 or 0.33 ng/kg/min) produced higher gallbladder ejection fractions compared to 0.02 μg/kg over 3 min (6.6 ng/kg/min). Which method is optimal requires further study.

Whether it is beneficial to routinely premedicate all patients or subgroups of patients with CCK also requires further research. Many authors have suggested that CCK pretreatment be reserved for patients who have fasted for longer than 24 hr (*1,4,6*). In these patients, gallbladders with patent cystic ducts may not fill with radiotracer (*12*) because they may be distended with increased intraluminal gallbladder pressure from biliary stasis or sludge and as a result have reduced radiotracer flow to the gallbladders. CCK causes these gallbladders to contract, decreasing the intraluminal pressure, and thereby permitting radiotracer to fill the gallbladder. If this suggestion was valid, then many patients in our study group received CCK pretreatment appropriately, since the average patient fasted for longer than 24 hr (Table 1).

We suggest the following imaging protocol for the diagnosis of acute cholecystitis. Premedicate with sincalide only those patients who have fasted for more than 24 hr. Use 0.01 μg/kg sincalide injected over 3 min (*9*). Inject radiotracer 20 min later and image for 1 hr. If there is no gallbladder filling within 1 hr, then inject 0.04 mg/kg of intravenous morphine and continue imaging for 30 min. Inject a second dose of radiotracer before morphine administration as necessary.

By using this protocol, one of the following outcomes will occur: (a) if there is gallbladder filling within 1 hr then there is no need for pharmacological intervention in many of the patients. More likely, the patient has a normal gallbladder or chronic cholecystitis, and only rare patients will have acute acalculous cholecystitis (in our study, three patients with diabetes and end-stage renal disease and one immunosuppressed patient); (b) if the gallbladder is visualized after intravenous morphine, then the patient has a patent cystic duct and most likely has chronic cholecystitis, although occasional cases of early acute cholecystitis are possible; and (c) if there is gallbladder nonvisualization 30 min after morphine injection, then the patient has an obstructed cystic duct and acute cholecystitis, but other causes of cystic duct obstruction should be excluded.

In our study, there was an unexpected association of false-

negative scans with diabetes and end-stage renal disease in three patients that may warrant further investigation. These three patients had acute acalculous cholecystitis with patent cystic ducts. We postulate that acute acalculous cholecystitis in these patients may be related to the small vessel disease of diabetes, producing focal ischemia and necrosis in distended gallbladders. The fourth patient with a false-negative scan was immunosuppressed and immunosuppression may have prevented the cystic duct obstruction that is usually associated with acute cholecystitis. If we had confined our analysis to patients who underwent surgery and did not have end-stage renal disease or immunosuppressive therapy, the sensitivity for detecting acute cholecystitis would have increased from 69% to 100% using strict criteria, and 71% to 85% using liberal criteria.

CONCLUSION

Pretreatment with 0.02 μg/kg CCK injected over 3–5 min followed by only 90 min of imaging was insufficient to identify all patent cystic ducts. The additional use of morphine augmentation increased significantly the detection of patent cystic ducts. This increased the positive predictive value and specificity of cholescintigraphy.

REFERENCES

1. Fink-Bennett D. Augmented cholescintigraphy: its role in detecting acute and chronic disorders of the hepatobiliary tree. *Semin Nucl Med* 1991;21:128–139.
2. Eikman EA, Cameron JL, Colman M, et al. A test for patency of the cystic duct in acute cholecystitis. *Ann Intern Med* 1975;82:318–322.
3. Freeman LM, Sugarman LA, Weissman HS. Role of cholecystokinetic agents in ^{99m}Tc-IDA cholescintigraphy. *Semin Nucl Med* 1981;11:186–193.
4. Kim CK, Tse KKM, Juweid M, et al. Cholescintigraphy in the diagnosis of acute cholecystitis: morphine augmentation is superior to delayed imaging. *J Nucl Med* 1993;34:1866–1870.
5. Fink-Bennett D, Balon H, Robbins T, et al. Morphine-augmented cholescintigraphy: its efficacy in detecting acute cholecystitis. *J Nucl Med* 1991;32:1231–1233.
6. Freitas JE, Coleman RE, Nagle CE, et al. Influence of scan and pathologic criteria on the specificity of cholescintigraphy: concise communication. *J Nucl Med* 1983;24: 876–879.
7. 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.
8. Mesgarzadeh M, Krishnamurthy GT, Bobba VR, Langrell K. Filling, postcholecystokinin emptying and refilling of normal gallbladder: effects of two different doses of CCK on refilling: concise communication. *J Nucl Med* 1983;24:666–671.
9. Krishnamurthy S, Krishnamurthy GT. Gallbladder ejection fraction: a decade of progress and future promise [Editorial]. *J Nucl Med* 1992;33:542–544.
10. Ziessman HA, Fahey FH, Hixson DJ. Calculation of gallbladder ejection fraction: advantage of continuous sincalide infusion over the 3-min infusion method. *J Nucl Med* 1992;33:537–541.
11. Swayne L, Palace F, Rothenberg J, Heitner D, Trivino J. Sensitivity, specificity and accuracy of CCK cholescintigraphy in acalculous biliary disease [Abstract]. *J Nucl Med* 1986;27:882.
12. Larsen MJ, Lingensmith WC III, Kuni CC. Radionuclide hepatobiliary imaging: non-visualization of the gallbladder secondary to prolonged fasting. *J Nucl Med* 1982;23:1003–1005.

EDITORIAL

Pharmacologic Intervention for the Diagnosis of Acute Cholecystitis: Cholecystokinin Pretreatment or Morphine, or Both?

Cholecystokinin (CCK) preadministration in conjunction with cholescintigraphy (using ^{131}I-rose bengal or ^{99m}Tc-dihydrothioctic acid) for the diagnosis of acute cholecystitis was first reported in 1975 by Eikman et al. (*1*). The authors attributed the improved efficacy of cholescintigraphy in their series in part to CCK pretreatment.

After introduction of ^{99m}Tc-iminodiacetic acid agent for cholescintigraphy (*2*), Weissmann et al. demonstrated that delayed imaging up to 4 hr increases the efficacy of the study compared to 1 hr imaging (*3*). Previous reviews indicated that CCK pretreatment can be used to shorten the imaging time from 4 hr to 60–90 min (*4–6*). On this basis, Chen et al. (*7*) present their evaluation, in this issue of the *Journal of Nuclear Medicine*, of whether 90 min of imaging after CCK pretreatment is sufficient to identify all patent cystic ducts, and whether addition of morphine augmentation improves the efficacy of cholescintigraphy. The article by Eikman et al. (*1*) was cited as a reference in one of the reviews and by Chen et al. Otherwise, no data seem to be available in the literature to support the above claim.

This issue deserves further clarification. Eikman et al. (*1*) did not imply that delayed imaging was unnecessary by stating, "Simple visual inspection of the images at 90 min was sufficient." Instead, their point was that *early images or quantitative analysis (from 110 min continuous acquisition) were unnecessary.* Also, they did not imply that delayed imaging was unnecessary by stating, "The improved reliability of the test is attributed to CCK pretreatment." The point was that *compared to detection of acute cholecystitis with conventional contrast radiologic technique*, improved detection is attributed to the use of CCK and, possibly, to the great sensitivity of the gamma camera. Delayed imaging was not even a routine part of the cholescintigraphy in 1975.

CCK pretreatment has been shown to be useful in certain conditions, although whether or not it obviates the need for delayed imaging cannot be answered at this time. In a series by Rosenthall et al., preadministration of CCK reduced false-positive results in patients with chronic cholecystitis (*8*). CCK pretreatment can be helpful in conditions in which functional resistance to tracer inflow may result from distention of gallbladder with viscous contents, such as during a prolonged fasting state, alcoholism and total parenteral nutrition (*9,10*). Kim et al. previously showed that approximately 50% of volunteers who had paired studies (without and with CCK pretreatment) showed more vigorous gallbladder filling after CCK pretreatment (*11*). Therefore, it can be stated that CCK will improve the efficacy of cholescintigraphy to some degree as compared to no pretreatment. Nevertheless, CCK pretreatment of all patients does not appear to have gained wide acceptance. At least fasting for 24 hr or longer appears to have become a routine indication to preadminister CCK in many laboratories.

MORPHINE AUGMENTATION

Following the introduction of morphine-augmented cholescintigraphy as an alternative to delayed imaging in 1984 by Choy et al. (*12*), several reports have been published on this subject (*13–17*). In most reports, morphine augmentation has been recommended primarily because of its logistic advantage but not necessarily because of its superior diagnostic accuracy. The general

Received Oct. 9, 1996; accepted Dec. 30, 1996.
For correspondence or reprints contact: Chun K. Kim, MD, Division of Nuclear Medicine, Mount Sinai Medical Center, One Gustave L. Levy Place, New York, NY 10029.