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Use of morphine cholescintigraphy in the diagnosis of acute cholecystitis in critically ill patients

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Abstract *Objective:* To determine the efficacy of morphine enhanced radionuclide cholescintigraphy (MC) in the diagnosis of acute cholecystitis (AC) in critically ill patients.
Design: Retrospective chart review.
Setting: 2 university hospitals.
Patients and methods: Records of all ICU patients who underwent MC as part of an evaluation for AC over an 8 year period were reviewed ($n = 45$). All patients initially had standard radionuclide cholescintigraphy (RC) performed which showed nonvisualization of the gallbladder (GB) and were then given morphine sulfate (0.05–0.1 mg/kg iV).
Results: The mean age was 54 years (range 18–84 years). Risk factors for AC included fasting in 41 patients (mean 12.4 days) and total parenteral nutrition in 32 patients. Signs of biliary sepsis included temperature >100 °F in 38 patients, WBC > 10000/ml^3 in 40 patients, abdominal pain in 29 patients, and abnormal liver fuction tests in 42 patients. 23 patients had GB ultrasonography, with 7 showing stones. MC was positive (non-visualization) in 16 patients and negative (GB visualized) in 29, including 4 with gallstones. All patients in whom the GB was visualized did so within 1 h. There were 13 patients with positive MC who underwent operation; 12 had AC (9 acalculous, 3 calculous). Three patients were treated medically and recovered (false positive). All 29 patients with negative MC were true negatives. Overall, MC had an accuracy of 91%, sensitivity of 100%, specificity of 88%, positive predictive value of 75%, and negative predictive value of 100%.
Conclusion: MC is a useful test in the evaluation of critically ill patients for suspected AC, particularly in patients with known risk factors or documented gallstones.

Key words Cholescintigraphy · Radionuclide cholescintigraphy · Morphine cholescintigraphy · Acute cholecystitis · Acalculous cholecystitis · Critical illness · Intensive care unit

Introduction

Acute cholecystitis, both calculous and acalculous, is being increasingly seen as a complication in critically ill patients [1–6]. While its precise etiology and pathophysiology are unknown, decreased mucosal perfusion associated with shock, an increase in bile viscosity and lithogenicity secondary to stasis, prolonged fasting, total parenteral nutrition, and narcotics have been proposed [4–8].

Establishing the diagnosis of acute cholecystitis in critically ill patients can be very difficult. Symptoms and physical signs may be obscured because of old age, altered

sensorium, immunosuppression, medications, or associated medical conditions, while other objective findings such as fever, leukocytosis, and abnormal liver function tests, tend to be nonspecific and unreliable. This lack of specificity can lead to substantial delays in diagnosis and therapy which contribute to multisystem organ dysfunction and death in up to 60% of patients [1–6].

The problems associated with accurately establishing the diagnosis of acute cholecystitis in this group of patients have led to an increased reliance by clinicians on radiologic imaging studies [9–12]. Routine imaging techniques such as ultrasonography, computed tomography, and radionuclide cholescintigraphy (RC) are often no more specific than clinical features and have been associated with a high incidence of false positive results [9, 13–16].

For over a decade, RC with Tc-99m labelled compounds has been used to confirm the diagnosis of acute cholecystitis in selected patients with right upper quadrant pain [9–12]. When this technique has been more broadly applied to unselected patients with nonspecific abdominal pain, prolonged fasting, pancreatitis, alcoholism, hepatocellular disease, severe intercurrent illness, or who were receiving total parenteral nutrition, an incidence of false positive results approaching 40% has been reported [9, 13–16].

In 1984, Choy et al. described improved accuracy of RC with the use of intravenous morphine sulfate (IV-MS) to enhance gallbladder filling [17]. Subsequent to this, we have successfully employed morphine augmented RC (MC) in the evaluation of critically ill surgical patients with suspected biliary sepsis [18–20]. The present report describes our accumulated experience with the use of MC in 45 critically ill patients with suspected acute cholecystitis over an 8 year period.

Materials and methods

A retrospective review was conducted of all intensive care unit (ICU) patients at the Robert Wood Johnson University Hospital, New Brunswick, New Jersey from July 1984–June 1989 and The Ohio State University Hospitals, Columbus, Ohio from July 1989–May 30, 1992, who underwent MC as part of a diagnostic evaluation for acute cholecystitis. The time periods studied corresponded to the period that one author (LF) practiced at each institution. Of these patients, 45 were identified and form the basis of this report. Of these patients, 25 have been previously reported [18–20]. During this period, approximately 900 cholescintigrams were performed on inpatients and 10000 patients were admitted to the surgical ICUs of these institutions, for an incidence of approximately 0.45% among surgical ICU patients.

The medical records of each patient were reviewed and abstracted for the following information: age, sex, admission, diagnosis, presence of risk factors (fasting, total parenteral nutrition), clinical signs of sepsis (fever, leukocytosis, abdominal pain), liver function tests (bilirubin, alkaline phosphatase, serum glutamic-oxaloacetic transaminase (SGOT), serum glutamic-pyruvic transaminase (SGPT), gamma glutamyl transferase (GGTP), with values >105% of upper limit of normal range considered abnormal), length of ICU stay prior to MC, use and results of ultrasonography, treatment, operative findings, and outcome.

Technique for MC: All patients initially underwent standard RC with 2–4 mCi of a Tc-99m iminodiacetic acid (IDA) derivative, (DISIDA or PIPIDA). Using a scintillation camera with a low energy, high resolution collimator, serial anterior views of the abdomen then given an injection of intravenous MS (0.05–0.1 mg/kg) if the gallbladder failed to visualize but the bowel had visualized during that time. Serial images were then obtained for up to 150 min.

Sensitivity, specificity, positive and negative predictive value, and accuracy of MC were determined using standard formulae. True positive results of MC were defined as those patients with persistent non-visualization of the gallbladder who had acute cholecystitis; true negatives, those with visualization of the gallbladder who did not have cholecystitis; false positives, those with nonvisualization of the gallbladder who did not have cholecystitis; and false negatives, those with visualization of the gallbladder who had cholecystitis. For comparison of RC with MC, all patients entering the study were considered "positives" by virtue of their demonstrating nonvisualization of the gallbladder on initial RC (a "positive" study) and later subdivided into true or false positives based on the presence or absence of acute cholecystitis. By the nature of the study design, there were no "negatives" for routine RC available for comparison with MC.

Results

The clinical features of the 45 patients (33 men, 12 women, mean age 54 years) reviewed are summarized in Table 1.

Reasons for admission to the ICU included trauma/burns in 16 patients; cardiac disease, 9 patients; ruptured abdominal aortic aneurysm/peripheral vascular disease, 8 patients; gastrointestinal hemorrhage, 3 patients; sepsis, 3 patients; and miscellaneous reasons, 6 patients. Signs of sepsis consistent with a biliary source included fever in 38 (84%) patients, leukocytosis in 40 (89%), abnormal liver function tests in 42 (93%), and abdominal tenderness in 29 (65%). Risk factors included critical illness in all patients, prolonged fasting from four to more than 42 days (mean: 12.4 days) in 41 (91%) patients, and administration of total parenteral nutrition in 32 (71%).

Table 1 Clinical features of 45 critically ill patients undergoing morphine cholescintigraphy

	N (%)
Mean age (years)	54
Prolonged fasting	41 (91)
TPN	32 (71)
Fever (>100 °F)	38 (65)
Leukocytosis (WBC>10^3/ml^3)	40 (89)
Abnormal LFTs[a]	42 (93)
Abdominal pain	29 (65)
US gallbladder/stones present	23/7

TPN total parenteral nutrition; *LFT's* liver function tests; *US* ultrasonography

[a] Any abnormal LFT

Table 2 Results of morphine cholescintigraphy in critically ill patients

True positive	12
True negative	29
False negative[a]	4
False positive	0
Sensitivity	1.0
Specificity	0.88
Positive predictive value	0.75
Negative predictive value	1.0
Accuracy	0.91

[a] Includes 3 patients treated nonoperatively with antibiotics that recovered

Ultrasonography was performed in 23 (51%) patients, and gallstones were documented in 7 (30%). After RC failed to show visualization of the gallbladder and IV-MS was administered, the gallbladder was visualized in 29 patients (64%). Thirteen of the 16 patients exhibiting nonvisualization after IV-MS underwent operation; 12 had acute cholecystitis (9 acalculous, 3 calculous), and one did not have gallbladder disease. The remaining three patients demonstrating nonvisualization of the gallbladder were not operated and recovered (considered false-positives). Only one of the seven patients with preoperatively documented gallstones had acute cholecystitis. All 29 patients with negative MC studies were true negatives. Visualization of the gallbladder occurred within 60 min of the administration of IV-MS in all patients. Overall, there were 12 true positives, 29 true negatives, four false-positive and no false-negative studies. Thus, MC had a sensitivity of 100%, a specific of 88%, a positive predictive value of 0.75, a negative predictive value of 1.0, and an overall accuracy of 91% (Table 2).

There were no complications related to the use of intravenous morphine documented in these patients. The majority of patients had received intravenous narcotics previously during their hospitalization. Prior exposure to intravenous morphine or other narcotics has not hampered the performance or interpretation of this test.

Discussion

Radionuclide cholescintigraphy has been valuable adjunct in the diagnosis of acute cholecystitis. Non-visualization of the gallbladder after administration of a radionuclide tracer is considered indicative of cystic duct obstruction and, therefore, felt to be diagnostic of acute cholecystitis. Initial reports using RC claimed a 98% accuracy and 100% specificity in symptomatic patients [9–12]. However, as the use and application of RC became more widespread, so have reports documenting less sensitivity, specificity, and accuracy in unselected patients with abdominal pain, especially those with alcoholism, prolonged fasting, pancreatitis, hepatocellular disease, critical illness, and those receiving total parenteral nutrition [13–16, 21]. These results have been improved with the use of delayed views [22].

Shuman et al. [15] reviewed their experience in 200 hospitalized patients who were studied for cholestasis or acute cholecystitis. Of the 41 patients hospitalized for complications of alcoholism 60% and 92% of the 17 patients receiving total parenteral nutrition demonstrated delayed or non-visualization of the gallbladder in the absence of physical or clinical evidence of acute cholecystitis. Similarly, Warner et al. [16] reported gallbladder nonvisualization in 18 of 50 patients [38%] who were fasting or received total parenteral nutrition and had no clinical evidence of acute cholecystitis.

The reason that the gallbladder does not fill in these patients is unclear, but may be related to altered biliary dynamics. Gallbladder stasis, with reabsorption of water from the bile, may cause the gallbladder to become dilated and filled with viscous, inspissated bile which simulates obstruction, preventing entry of the radionuclide into the gallbladder while maintaining flow through the common bile duct. Abnormal bile production due to hepatocellular dysfunction may also result in abnormal clearance of the Tc-99m IDA derivatives resulting in nonvisualization of the biliary tree [13, 15, 16].

Injection of intravenous morphine sulfate causes contraction of the sphincter of Oddi, which has been reported to produce up to a tenfold increase in resting common bile duct pressure [23]. In 1984, Choy et al. [17] reported the use of IV-MS (0.1 mg/kg) to promote gallbladder filling in 59 unselected patients with a clinical diagnosis of acute cholecystitis who demonstrated nonvisualization of the gallbladder after 40 min during routine RC. Diagnostic accuracy increased to 98% and specificity to 100%. They suggested that the morphine increased common bile duct pressure sufficiently to overcome the partial or functional cystic duct obstruction, resulting in a decreased incidence of false-positive (non-visualization) scans. These results were corroborated in an earlier report by Flancbaum and Alden [19] involving 30 patients who underwent MC for acute abdominal pain and 13 patients hospitalized for non-biliary tract disease who had factors associated with a high rate of false positive scans. In those patients, the diagnosis of acute cholecystitis was reliably confirmed in 100% and excluded in 90%. Thus, MC had a sensitivity of 97%, a specificity of 100%, a positive predictive value of 1, a negative predictive value of 0.94, and 98% accuracy in that series.

The incidence of acute cholecystitis appears to be increasing in critically ill patients. In these patients, where clinical findings are subtle and diagnostic tests non-specific, a delay in diagnosis and a high mortality are the rule. Radionuclide cholescintigraphy has been falsely positive in over one-third of critically ill patients with suspected acute cholecystitis [14]. In a preliminary report of 18 critically ill patients with suspected biliary sepsis

Flancbaum et al. [18] found that MC reliably excluded the acute cholecystitis in 17 patients. The remaining patient demonstrated persistent non-visualization after IV-MS and had acalculous cholecystitis. Since then, the number of critically ill patients evaluated for occult sepsis with MC has been increased to 45. All had clinical findings suggestive of a biliary source; seven had sonographically documented gallstones. Following administration of IV-MS, the scan demonstrated gallbladder filling in 29 patients, none subsequently proved to have acute cholecystitis. There were 16 patients who had persistent non-visualization after MC; 12 had acute cholecystitis at operation (9 calculous, 3 acalculous). One patient did not have acute cholecystitis at operation (false positive), and 3 patients with non-visualization were treated medically and improved (also considered false positives).

Of interest is the observation that only 3 of 7 patients with gallstones had acute cholecystitis. Cholestasis, hepatic dysfunction, and jaundice, are common in these patients and may not be due to the presence of gallstones or obstruction. Thus, in this group of patients with acute cholecystitis, the presence of gallstones may be an incidental finding, with the etiology and pathogenesis of the acute cholecystitis being that of acalculous cholecystitis.

There are limitations to the interpretation of these results. This is a retrospective study and pathologic data are only available on those patients who underwent surgery. The designation of patients as "true negatives" was based upon the resolution of their clinical symptoms with medical management or the determination of a definitive alternate etiology for their sepsis. Because acalculous cholecystitis has been associated with a high incidence of gangrene, up to 50%, in previous series [1–7], we feel that it is unlikely that any of the patients classified as "true negatives" had acalculous cholecystitis and improved on antibiotics alone, in the absence of cholecystectomy or cholecystostomy. In addition, all patients with persistent non-visualization of the gallbladder after morphine augmentation were considered "false positives", based upon the same assumption that they would not have recovered with antibiotic treatment alone.

Given the limitations discussed above, the use of MC improved the overall diagnostic accuracy of RC in this group of critically ill patients from 45–50% reported in the literature to 91%. There were only 4 false-positive studies, yielding an overall positive predictive value of 0.75 and a negative predictive value of 1.0, with a sensitivity of 100% and a specificity of 88%. MC reduced the false positive rate with standard RC from 35–50% reported in the literature [13–16], and as would have been seen in this series, 73% (33 out of 45 cases), to 12%. The positive predictive value was improved from 0 to 0.75, and the negative predictive value improved from 0.8 to 1.0. Additionally, the gallbladder filled by 1 h after IV-MS administration in all 29 patients who eventually visualized, eliminating the need for delayed views and prolonged stays in the radiology department for the sicker patients.

These results suggest that MC is a useful technique in critically ill patients with suspected acute cholecystitis. It is particularly helpful in excluding the diagnosis in those patients who are fasting, receiving total parenteral nutrition, or have documented gallstones.

References

1. Winegarner FG, Jackson GF (1971) Posttraumatic acalculous cholecystitis: a highly lethal complication. J Trauma 11:567–569
2. Long TN, Heimback DM, Carrico CJ (1978) Acalculous cholecystitis in critically ill patients. Am J Surg 136:31–36
3. Orlando R, Gleason E, Drezner AD (1983) Acute acalculous cholecystitis in the critically ill patient. Am J Surg 145:472–476
4. Flancbaum L, Majerus TC, Cox EF (1985) Acute post traumatic acalculous cholecystitis. Am J Surg 150:252–256
5. Fabian TC, Hickerson WL, Mangiante EC (1986) Posttraumatic and postoperative acute cholecystitis. Am Surg 52:188–192
6. Wilton PB, Delaney JP (1987) Acute acalculous cholecystitis in the intensive care unit. Surgical Rounds 10:30–46
7. Peterson SR, Sheldon GF (1979) Acute acalculous cholecystitis: a complication of hyperalimentation. Am J Surg 138:814–817
8. Doty JE, Pitt HA, Porter-Fink V, DenBesten L (1984) The effect of intravenous fat and total parenteral nutrition on biliay physiology. J Parenter Enter Nutr 8:263–268
9. Laing FC (1963) Diagnostic evaluation of patients with suspected acute cholecystitis. Radiol Clin North Am 21: 477–493
10. Susarez CA, Block F, Bernstein D, Serafini A et al (1980) Role of HIDA/PIPIDA scanning in diagnosing cystic duct obstruction. Ann Surg 191: 391–396
11. Weissman HS, Frank MS, Berstein LH, Freeman LM (1979) Rapid and accurate diagnosis of acute cholecystitis with Tc-99m-HIDA cholescintigraphy. AJR 132:523–528
12. Szlabick RE, Catoo JE, Fink-Bennett D, Ventura V (1980) Hepatobiliary scanning in the diagnosis of acute cholecystitis. Arch Surg 115:540–544
13. Kalfe V, Forelich JW, Lloyd R, Thrall JH (1993) Predictive value of an abnormal hepatobiliary scan in patients with severe intercurrent illness. Radiology 146:191–194
14. Garner WL, Marx MV, Fabri PJ (1988) Cholescintigraphy in the critically ill. Am J Surg 155:727–729
15. Shuman WP, Gibbs P, Rudd TG, Mack LA (1982) PIPIDA scintigraphy for cholecystitis: false positives in alcoholism and total parenteral nutrition. AJR 138:1–5
16. Warner BW, Hamilton FW, Sibserstein EB et al (1987) The value of hepatobiliary scans in fasted patients receiving total parenteral nutrition. Surgery 102:595–600
17. Choy D, Shi E, Mclean RG et al (1984) Cholescintigraphy in acute cholecystitis: use of intravenous morphine. Radiology 151:203–207

18. Flancbaum L, Alden SM, Trooskin SZ (1989) Use of cholescintigraphy with morphine in critically ill patients with suspected cholecystitis. Surgery 106: 668–674
19. Flancbaum L, Alden SM (1990) Morphine cholescintigraphy. Surg Gynecol Obstet 171:227–232
20. Flancbaum L, Wilson GA, Choban PS: Morphine cholescintigraphy in hospitalized patients: the significance of a positive result. Surg Gynecol Obstet (in press)
21. Shuman WP, Mack LA, Rudd TG et al (1982) Evaluation of acute right upper quadrant pain: sonography and Tc-99m-PIPIDA cholescintigraphy. AJR 139:61–64
22. Weissman HS, Sugarman LA, Badia JD, Freeman LM (1980) Improving the specificity and accuracy of Tc-99m-IDA cholescintigraphy with delayed views. (Abstr) J Nucl Med 21:17
23. Murphy P, Salomon J, Roseman D (1980) Narcotic anesthetic drugs and their effect of biliary dynamics. Arch Surg 115:710–711

ANNOUNCEMENTS

1995

Second European Postgraduate Course in Neonatal and Pediatric Intensive Care Medicine

16–18 March, Berne, Switzerland
Information: Administrative Secretariat: Barbara Bühlmann, Congress and Business Services, Postfach 316, CH-3000 Bern 25, Switzerland
Phone: +41-31-331-82
Fax: +41-31-332-9879

15th International Symposium on Intensive Care and Emergency Medicine

21–24 March, Brussels, Belgium
Information: Secretariat, Prof. J.L. Vincent, Department of Intensive Care, Erasme University Hospital, Route de Lennik 808, B-1070 Brussels, Belgium
Phone: +32-2-555-3215
Fax: +32-2-555-4555

First International Congress of Anaesthesiology and Intensive Care in Developing Countries

19–21 April, Lusaka, Zambia
Information: Dr. Alisher Agzamov, UTH Board, Private Bag RW 1X, Ridgeway 15102, Lusaka, Zambia
Tel.: 250305/227709-21
Fax: 263805

8th Congress of the Western Pacific Association of Critical Care Medicine

21–24 April, Kuala Lumpur, Malaysia
Information: Critical Care 1995, P.O. Box 331, Jalan Sultan, 46740 Petaling Jaya, Selangor, Malaysia
Phone: (603)-7550-455
Fax: (603)-7556-715

7th International Intensive Care Symposium

5–6 May, Istanbul, Turkey
Information: F. Esen, MD, Department of Anesthesiology and Intensive Care, University of Istanbul, Faculty of Medicine, Çapa Klinikleri, TR-34390 Istanbul, Turkey
Tel.: 90-212-631-8767 or 90-212-531-3126
Fax: 90-212-533-2083

5th Vienna Shock Forum

7–11 May, Vienna, Austria
Information: Prof. Dr. G. Schlag, Ludwig Boltzmann Institut für Experimentelle und Klinische Traumatologie, Donaueschingenstrasse 13, A-1200 Vienna, Austria
Phone: +43-1-331 10-464 or 469
Fax: +43-1-331 10-460

10th European Congress of Neurosurgery

7–12 May, Berlin, Germany
Information: Prof. Dr. M. Brock, Congress President, Department of Neurosurgery, Universitätsklinikum Steglitz, Hindenburgdamm 30, D-12203 Berlin, Germany
Fax: 0049-30-798-3569

11th Greek Congress of Anaesthesiology

24–28 May, Island of Corfu, Greece
Information: Congress Secretariat, Aeolos Congresses, 93, Falirou Str., GR-11741 Athens, Greece
Phone: 01-924-1945/6
Fax: 01-924-1974

2nd International Conference on Sepsis in the ICU – A Masterclass Symposium

27–29 June, Maastricht, The Netherlands
Information: The Secretariat, Castle House Conferences, 28–30 Church Road, Tunbridge Wells, Kent TN1 1JP, UK
Phone: +44-892-539-606
Fax: +44-892-517-005

3rd International Congress of the Society of Organ Sharing

17–19 July, Paris, France
Information: Secretariat Office, France-Transplant, Hôpital St. Louis, 1 Avenue Claude Vellefaux, F-75475 Paris Cedex 10, France
Fax: +33-1-4206-9490

24th Central European Anaesthesia Congress

4–8 September, Vienna, Austria
Information: Udo M. Illievich, MD, Secretary, P.O. Box 52, A-1097 Vienna, Austria
Fax: +43-1-406-4811

8th European Congress on Intensive Care Medicine

18–22 October, Athens, Greece
Information: Prof. Ch. Roussos (Organizing Committee President), Evangelismos Hospital, Critical Care Department, 45–47 Ipsilandou St., GR-106 76 Athens, Greece
Tel.: +301-724-3320
Fax: +301-721-6503
or Congress Secretariat: Triaena Congress, 24, Har. Trikoupi St., GR-106 79 Athens, Greece
Tel.: +301-360-9511-15 or 360-9552
Fax: +301-360-7962

International Symposium: 66 Years of Surfactant Research

5–10 November. The scientific sessions will be held at the universities of Vienna and Budapest with poster sessions on board ship. Accommodation will be on board ship from Passau (Germany) along the river Danube via Vienna (Austria) to Budapest (Hungary).
Information: Prof. Dr. B. Lachmann, Department of Anaesthesiology, Erasmus University Rotterdam, P.O. Box 1738, NL-3000 DR Rotterdam, The Netherlands
Phone: +31-10-4087-312
Fax: +31-10-4367-870

1996

9th European Congress on Intensive Care Medicine

23–27 September, Glasgow, UK
Information: Secretariat: Castle House Conferences, 28–30 Church Road, Turnbridge Wells, Kent TN1 1JP, UK.
Tel.: +44-1892-539606;
Fax: +44-1892-517005