Use of a Fatty Meal Cholecystagogue Protocol in Hepatobiliary Scintigraphy for Chronic Functional Gallbladder Disease

Justin G. Peacock[1,2], Horace A. Hayes[3], and Tylor D. Connor[3]

[1]Department of Radiology and the Radiological Sciences, Uniformed Services University, Bethesda, Maryland; [2]Department of Military Medical Operations, Armed Forces Radiobiology Research Institute, Bethesda, Maryland; and [3]Department of Radiology, Brooke Army Medical Center, San Antonio, Texas

CE credit: For CE credit, you can access the test for this article, as well as additional JNMT CE tests, online at https://www.snmmilearningcenter.org. Complete the test online no later than March 2027. Your online test will be scored immediately. You may make 3 attempts to pass the test and must answer 80% of the questions correctly to receive 1.0 CEH (Continuing Education Hour) credit. SNMMI members will have their CEH credit added to their VOICE transcript automatically; nonmembers will be able to print out a CE certificate upon successfully completing the test. The online test is free to SNMMI members; nonmembers must pay $15.00 by credit card when logging onto the website to take the test.

Chronic functional gallbladder disorder, characterized by biliary pain in the absence of structural pathology, poses a diagnostic challenge necessitating reliable cholecystagogues for accurate evaluation. However, recurrent shortages of synthetic cholecystokinin analogs have prompted the exploration of alternative agents. This paper describes the efficacy of Ensure Plus as a viable fatty meal substitute for hepatobiliary scintigraphy in assessing chronic functional gallbladder disorder. Through comparative studies, Ensure Plus demonstrates comparable diagnostic accuracy to cholecystokinin in similar patient populations. Furthermore, Ensure Plus demonstrates significant symptom improvement after cholecystectomy in patients with anomalous gallbladder ejection fractions. This paper offers a detailed protocol for the seamless integration of Ensure Plus into hepatobiliary scintigraphy, providing clinicians with a valuable tool to navigate cholecystokinin shortages while maintaining diagnostic precision in cases of chronic functional gallbladder disorder. The use of Ensure Plus not only addresses practical supply challenges but also underscores its potential as a cost-effective and clinically sound alternative in biliary diagnostics.

Key Words: hepatobiliary scintigraphy; chronic functional gallbladder disorder; gallbladder ejection fraction; fatty meal; Ensure Plus

J Nucl Med Technol 2024; 52:15–20
DOI: 10.2967/jnmt.123.266789

The gallbladder is a saccular organ attached to and extending along the underside of the liver (Fig. 1A). The primary function of the gallbladder is to serve as a reservoir for bile salts, lipids, and other macromolecules involved in the digestion of fats (*1*). Bile enters and exits the gallbladder via the cystic duct, which connects directly with the common hepatic duct to form the downstream common bile duct, which empties into the duodenum after passing through the pancreas and sphincter of Oddi (Fig. 1A). The sphincter of Oddi contracts between episodes of feeding to create back pressure within the biliary system, which results in retrograde passage of bile through the cystic duct into the gallbladder for storage. On feeding and neurohormonal stimulation, the smooth muscle within the muscularis layers of the gallbladder walls contracts and the sphincter of Oddi relaxes to allow for differential pressure dynamics that push bile out of the gallbladder, through the common bile duct, and out of the sphincter of Oddi to the duodenum. Cholecystokinin is the most potent hormonal stimulator of gallbladder smooth muscle contraction and sphincter of Oddi relaxation, but acetylcholine released from the vagal or enteric nerves can also produce a similar effect (*2–10*). Gallbladder functioning and the biliary system require patent ducts and effective management of pressure dynamics to ensure that bile is appropriately delivered from the gallbladder to the food bolus. Disruption of the duct patency or biliary pressure dynamics will result in gallbladder pathology, including acute and chronic disease (Fig. 1B).

Obstruction of the biliary duct system or disruption of the smooth muscle dynamics involved in the passage of bile through the duct system results in common biliary pathologies (Table 1) (*1*,*11*). Acute blockage of biliary transit out of the gallbladder, usually from a gallstone, results in increased pressure within the gallbladder lumen and resultant inflammation throughout the gallbladder walls (acute calculous cholecystitis). This results in pain of the right upper quadrant along with other gastrointestinal symptoms. Rarely, a more serious form of acute cholecystitis can result without gallstone blockage (acalculous cholecystitis); this form is commonly secondary to gallbladder injury or systemic disease. Acute cholecystitis is commonly evaluated with ultrasound, but it can be confirmed or further assessed with hepatobiliary scintigraphy, CT, or MRI. On hepatobiliary scintigraphy, acute cholecystitis is

Received Oct. 1, 2023; revision accepted Nov. 9, 2023.
For correspondence or reprints, contact Justin G. Peacock (justin.peacock@usuhs.edu).
Published online Dec. 13, 2023.

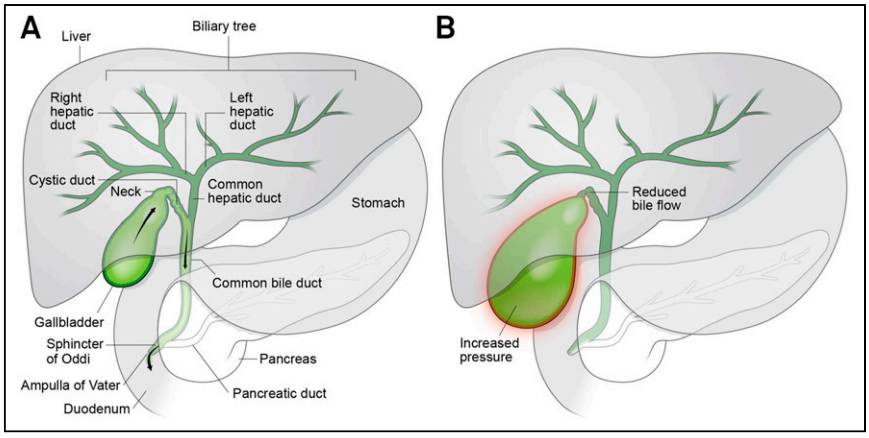

FIGURE 1. Normal and abnormal biliary transit. (A) Normal anatomy and physiology of hepatobiliary system, with hepatic production of bile, excretion via hepatic ducts, localization to gallbladder, and excretion, on stimulation, through common bile duct and ampulla of Vater to small bowel. Sphincter of Oddi acts as pressure valve for bile passing into small bowel near junction of biliary system and duodenum. (B) Reduced bile flow (which in case of chronic functional gallbladder disorder is due to gallbladder dysmotility), which results in increased pressure and inflammation within gallbladder (cholecystitis).

confirmed by blockage of radiopharmaceutical passing through the cystic duct to the gallbladder (*1*,*12*).

In contrast to acute cholecystitis cases, chronic cases of cholecystitis can develop in patients either through obstruction or through disruption of pressure dynamics in the biliary system. Like acute cholecystitis, chronic cholecystitis can also develop in the setting of gallstones (chronic calculous cholecystitis). Some cases of chronic gallbladder disease are also found in patients without gallstones (acalculous). Physicians and researchers have historically questioned whether chronic acalculous gallbladder disease, termed chronic functional gallbladder disorder, was a true entity (*13*,*14*). Chronic functional gallbladder disorder is defined as biliary pain without gallstones or other structural pathology (Fig. 1B) (*14–17*). Biliary pain is described as epigastric or right upper quadrant pain that builds up, occurs at different intervals, and is not significantly associated with bowel movement, position changes, or acid suppressants (*11*,*18*,*19*). It can result in nausea and vomiting and radiate to the back. Supportive evidence for chronic functional gallbladder disorder includes a low gallbladder ejection fraction on hepatobiliary scintigraphy, normal liver or pancreatic enzymes, and normal bilirubin (*11*,*12*,*14*,*20*). Mimicking physiologic biliary physiology, stimulated hepatobiliary scintigraphy can help to assess the gallbladder ejection fraction in cases of possible chronic functional gallbladder disorder. In this article, we will describe the history and use of a standardized fatty meal, Ensure Plus (Abbott), to determine gallbladder ejection fractions in possible cases of chronic functional gallbladder disorder.

BACKGROUND

Before hepatobiliary scintigraphy came into use, cholegraphy was performed with intravenous and oral contrast agents and radiographic or fluoroscopic imaging (*3*,*21*). During this time, researchers made discoveries regarding biliary physiology and pathogenesis that are important for hepatobiliary scintigraphy. Initial work on gallbladder contraction and biliary excretion resulted from cholegraphic studies in which patients were administered an oral cholecystagogue (*22–25*). Examples of the reported oral cholecystagogues include milk, corn oil emulsion, Cholex (egg yolk, soya lecithin, glycerin, and peanut oil), D-sorbitol solution, safflower oil emulsion, vegetable oil, fatty meal (Lipomul), and Ensure Plus (*5*,*8*,*12*,*22*,*23*,*25–33*). In 1957, cholecystokinin was developed as an intravenous cholecystagogue demonstrating prompt and strong contraction of the gallbladder and opening of the sphincter of Oddi (*2*,*3*). Beginning with the development of radiolabeled iminodiacetic acid analogs in 1976, followed

TABLE 1
Gallbladder/Biliary Pathologies, Common Symptoms, and Hepatobiliary Scintigraphy Findings

Pathology	Symptom	Finding
Acute calculous cholecystitis	Acute biliary colic with or without fever, nausea, vomiting	Nonvisualization of gallbladder
Acute acalculous cholecystitis	Critical illness, sepsis, jaundice, pain in right upper quadrant	Nonvisualization of gallbladder (variable false positive due to illness)
Chronic calculous cholecystitis	Variable: biliary colic, nausea, reflux, bloating	Delayed gallbladder ejection fraction; stones on hepatobiliary scintigraphy or ancillary imaging
Chronic functional gallbladder disorder	Variable: biliary colic, nausea, reflux, bloating	Delayed gallbladder ejection fraction (other reported signs not diagnostic)
Sphincter-of-Oddi syndrome	Biliary colic, nausea, vomiting	Radiopharmaceutical concentration in biliary tree; delayed bowel excretion
Enterogastric reflux	Epigastric pain, vomiting, nausea, heartburn	Reflux of radiopharmaceutical in bowel proximal to ampulla of Vater
Hepatic dysfunction	Pain in right upper quadrant; severe illness pending cause	Delayed extraction by liver and delayed excretion from liver

by ^{99m}Tc-mebrofenin, which demonstrated better hepatic extraction and decreased renal excretion, hepatobiliary scintigraphy gradually replaced oral cholegraphy for imaging functional gallbladder pathologies (*1*,*12*,*34–36*).

As a predominantly functional gallbladder pathology, chronic functional gallbladder disorder began to be characterized using cholecystagogues to determine gallbladder ejection fractions. Using different cholecystokinin administration protocols with hepatobiliary scintigraphy, researchers found the least variation in results with a 60-min continuous cholecystokinin infusion (*12*,*36*,*37*). Using this protocol, researchers found that the lower limit of normal gallbladder ejection fractions was 38%, with gallbladder ejection fractions less than 38% considered abnormal. Unfortunately, sincalide (the commercial analog of cholecystokinin) has been prone to shortages over the years; oral cholecystagogues have therefore been used to continue assessments for chronic functional gallbladder disorder (*38*). Among the oral cholecystagogues, milk, corn oil emulsions, Lipomul, and Ensure Plus have been investigated to assess for normal gallbladder ejection fractions (*8*,*26*,*29*,*39*). In adults, researchers found normal gallbladder ejection fractions to be at least 40% for milk after 60 min, at least 20% for corn oil emulsions after 60 min, and at least 33% for a fatty meal (i.e., Ensure Plus) after 60 min. In pediatric patients given Lipomul, researchers found normal gallbladder ejection fractions to be at least 35% after 30 min. Among these options, Ensure Plus is well tolerated, with a variety of flavors, consistent preparation (11.4 g of fat), and low lactose content (*8*). In contrast to sincalide administration, which occurs over 60 min, Ensure Plus is administered orally within 5 min and is better tolerated. Ensure Plus is much more affordable than compounded or commercial preparations of sincalide. Ensure Plus is also more accessible to any nuclear medicine practice.

In a comparison of cholecystokinin to Ensure Plus in hepatobiliary scintigraphy for suspicion of chronic functional gallbladder disorder, we found that patients receiving cholecystokinin or Ensure Plus did not significantly differ in the percentage of abnormal gallbladder ejection fractions identified in similar patient populations (*28*). The descriptive statistics from that same study found that the sensitivity, specificity, positive predictive value, and negative predictive value for chronic cholecystitis on histopathology or for a subjective reduction in postoperative biliary-type pain in patients undergoing cholecystectomy. Li et al. assessed the symptoms for patients undergoing hepatobiliary scintigraphy with Ensure Plus for suspected chronic functional gallbladder disorder, comparing the symptom outcomes after cholecystectomy or conservative management in patients with normal or abnormal gallbladder ejection fractions (*27*). In patients with abnormal gallbladder ejection fractions on Ensure Plus hepatobiliary scintigraphy, 97% experienced symptom improvement after cholecystectomy, compared with 65% who were treated conservatively. Although these are retrospective studies, these findings suggest that Ensure Plus can be used instead of cholecystokinin for gallbladder ejection fraction evaluation in suspected cases of chronic functional gallbladder disorder. This is particularly helpful during sincalide shortages and as a cost-saving measure. In this article, we will describe our institutional approach to using Ensure Plus as the cholecystagogue in hepatobiliary scintigraphy for evaluation of chronic functional gallbladder disorder.

Preparation

In preparation for Ensure Plus hepatobiliary scintigraphy for gallbladder ejection fraction, patients should fast for at least 2 h and preferably 4–6 h (*1*,*12*). Ingested food stimulates endogenous release of cholecystokinin, which can interfere with the hepatobiliary scintigraphy study. If the patient has been fasting for more than 24 h, bile and sludge can accumulate in the gallbladder and interfere with the passage of radiopharmaceutical into the gallbladder. For these patients, one can pretreat with sincalide. The Society of Nuclear Medicine practice guideline recommends pretreating patients with 0.02 μg/kg sincalide IV over 3–60 min, approximately 15–30 min before injecting the radiopharmaceutical (*12*). For pretreatment at our institution, we have found that sincalide administration over 3–5 min, 30 min before radiopharmaceutical administration, is sufficient. If sincalide is not available, a fatty meal can be given at least 2 h before the hepatobiliary scan for gallbladder ejection fraction. If patients have been fasting for more than 24 h, there may be other factors that may impact the accuracy of the gallbladder ejection fraction results, including systemic illness. In such patients, it may be advisable to postpone gallbladder ejection fraction imaging until the patient is more stable (*1*).

Additionally, it is important to withhold opiate medications for at least 6 h or 3–4 half-lives before Ensure Plus hepatobiliary scintigraphy for gallbladder ejection fraction (*12*). Opiates can result in inaccurate results due to their effects on the sphincter of Oddi. In some cases, the reversal agent, naloxone hydrochloride, can be administered.

Patients should be instructed to remain still and breathe normally during the imaging phases of the hepatobiliary scintigraphy study. They should avoid coughing, clearing their throat, taking deep breaths, or falling asleep.

Radiopharmaceutical

Historically, ^{99m}Tc-labeled iminodiacetic acid molecules, such as hepatobiliary iminodiacetic acid, were used for hepatobiliary scintigraphy, but because of poor uptake in cases of hyperbilirubinemia, they are no longer widely used (*1*). Currently, ^{99m}Tc-disofenin (2,6-diisopropylacetanilido iminodiacetic acid) and ^{99m}Tc-mebrofenin (bromo-2,4,6-trimethylacetanilido iminodiacetic acid) are approved for use in hepatobiliary scintigraphy. These radiopharmaceuticals have improved hepatic extraction, including in cases of elevated bilirubin levels up to 20–30 mg/dL (*1*). These bilirubin analogs are extracted by the liver and excreted through the biliary system on the basis of pressure dynamics with the biliary system (Fig. 1A). ^{99m}Tc-disofenin and ^{99m}Tc-mebrofenin are administered intravenously at activities of

111–185 MBq (3–5 mCi). In cases of hyperbilirubinemia, the activities can be raised to 185–370 MBq (5–10 mCi). For children, activities are weight-based, at 1.8 MBq/kg (0.05 mCi/kg) (*12*).

Cholecystagogue Precautions

Precautions for sincalide administration include standard allergic reactions and those related to the mechanism of action (*10*). Severe hypersensitivity reactions have been reported, including anaphylaxis. Sincalide has also been reported to induce preterm labor or abortion in pregnant patients because of effects on smooth muscles. Some patients report severe biliary colic symptoms, particularly patients with gallstones. If the pain is severe, it is recommended to stop sincalide infusion, report the symptoms, and continue imaging. For some surgeons, reproduction of the initial patient-reported symptoms during the scan is used as a positive factor for recommending cholecystectomy. Additional symptoms include nausea, vomiting, dizziness, and flushing.

Precautions for Ensure Plus predominantly involve allergic reactions. Patients with lactose intolerance generally do not have problems with Ensure Plus because of the low amounts of lactose in the formula (*40*). Patients with galactosemia, particularly severe galactosemia, should avoid Ensure Plus. As an oral agent, Ensure Plus may not be suitable for patients who cannot tolerate oral intake. Patients with gastric feeding tubes may undergo Ensure Plus hepatobiliary scintigraphy, but if the enteric tube is in a significantly postpyloric position, Ensure Plus may not have the intended effect on gallbladder contraction; this has not been studied.

Acquisition

After the patient is positioned supine with a pillow beneath the knees and arms on the sides and supported, the radiopharmaceutical (^{99m}Tc-disofenin or ^{99m}Tc-mebrofenin) is injected intravenously. Dynamic imaging with a large-field-of-view γ-camera and a low-energy all-purpose or low-energy high-resolution collimator ensures that the liver, gallbladder, biliary tree, and bowel can be simultaneously visualized (*12*). The optimal image matrix with such a collimator is 128 × 128. Dynamic imaging at a rate of 1 frame/min for 60 min is then performed. Within this time frame, the gallbladder should fill, and some radiopharmaceutical may pass into the bowel. If the gallbladder does not fill in 60 min, it is recommended to evaluate the patient for signs of acute cholecystitis. Repeat imaging could be obtained after sincalide pretreatment.

After pre–Ensure Plus imaging is completed, 237 mL (8 oz) of Ensure Plus is then administered by mouth to the patient. Ideally, the patient should try to drink the Ensure Plus within 5 min. The patient is then again positioned supine. At our institution, we then position the γ-camera detector in the left anterior oblique position and perform dynamic imaging at 30 s/frame for 120 frames. This approach allows for finer time resolution, but 1 min/frame for 60 frames would also suffice.

Processing

Pre– and post–Ensure Plus dynamic images are then processed to determine the gallbladder ejection fraction. A region of interest (ROI) is drawn around the gallbladder (Fig. 2). The individual who is processing the images should ensure that there is no significant gallbladder motion during the pre– or post–Ensure Plus dynamic imaging. If the gallbladder moves significantly outside the ROI during the scan, then the technologist cannot batch process the images and should instead process the images individually to ensure that the gallbladder lies within the ROI at each time point. The individual who is processing the images should also ensure that there is no significant biliary tree radiopharmaceutical overlap with the ROI over the course of dynamic pre– or post–Ensure Plus imaging. The counts from the ROI are then processed by the imaging software to generate a time–activity curve (Fig. 2). The gallbladder ejection fraction percentage is calculated from the maximum and minimum gallbladder ROI counts as [(maximum count − minimum count)/maximum count] × 100 (*12*).

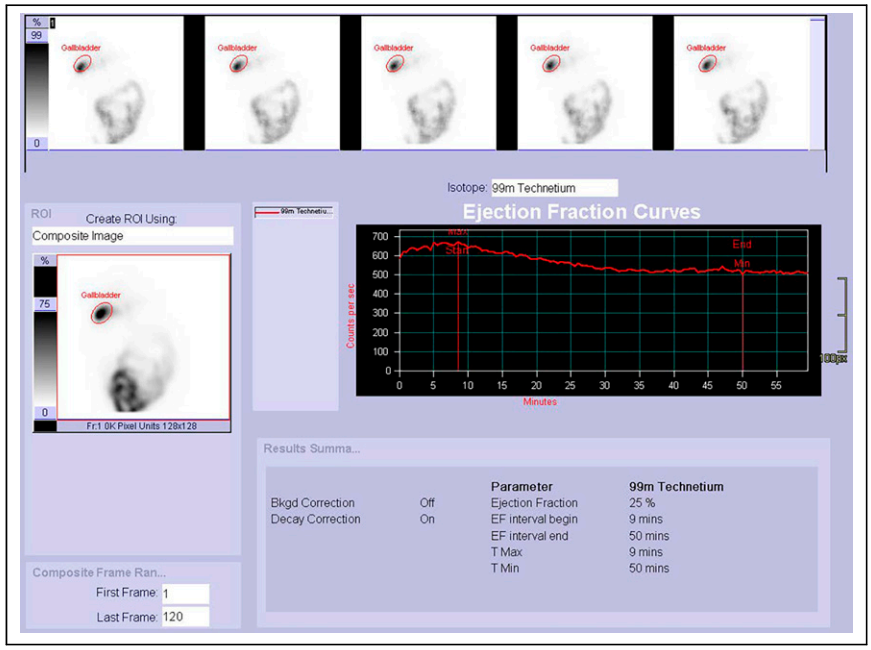

FIGURE 2. Ensure Plus hepatobiliary scintigraphy results for patient with chronic functional gallbladder disorder (gallbladder ejection fraction, 25%). Appropriate gallbladder ROI placement is shown. Ejection fraction was calculated from demonstrated time–activity curve. Low ejection fraction (<33%) is consistent with chronic functional gallbladder disorder. EF = ejection fraction; Fr:1 = frame 1; T max = time of maximum counts/s; T min = time of minimal counts/s.

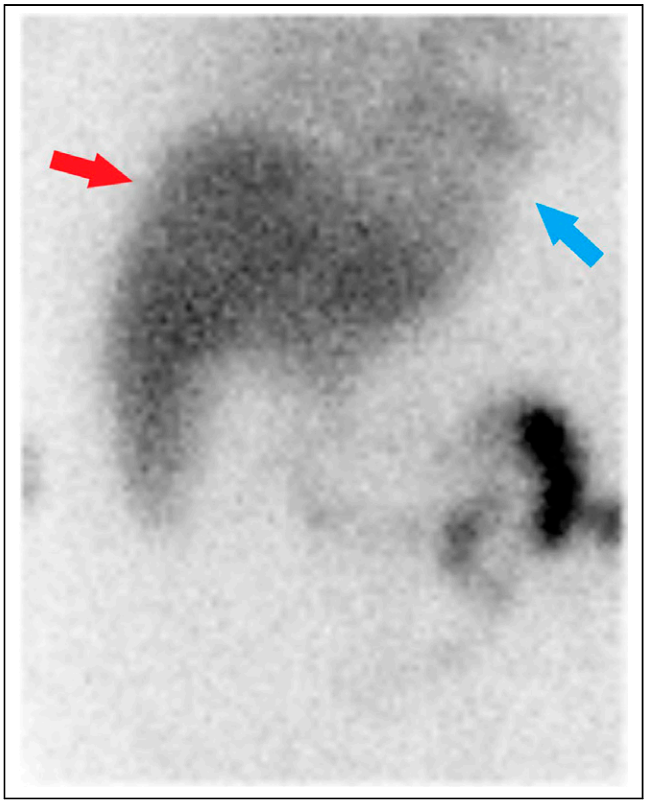

FIGURE 3. In this patient with severe hepatic dysfunction, image at 60 min after ^{99m}Tc-mebrofenin injection demonstrates significant persistent uptake in cardiac blood pool (blue arrow) and liver (red arrow), with little passage into bowel and nonvisualization of gallbladder.

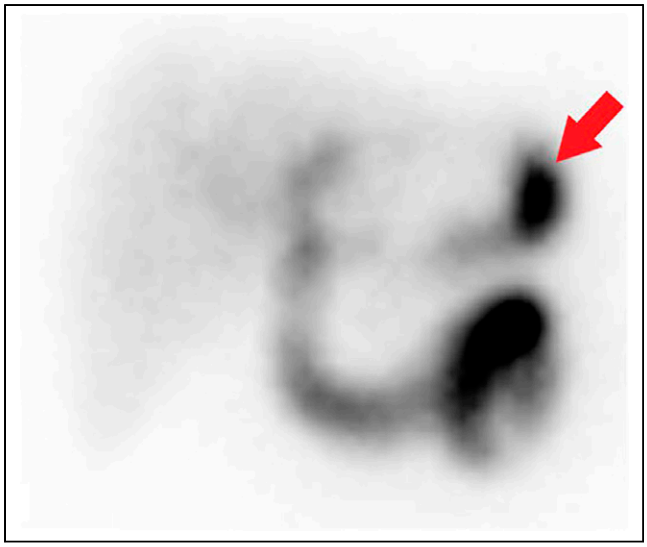

FIGURE 4. In this selected hepatobiliary scintigraphy image 40 min after injection of ^{99m}Tc-mebrofenin, there is moderate reflux (arrow) of radiopharmaceutical in retrograde fashion to stomach. Enterogastric reflux can be cause of abdominal symptoms in patients and should be reported if seen.

Interpretation

Interpretation of the Ensure Plus hepatobiliary scintigraphy for gallbladder ejection fraction involves evaluating the pre–Ensure Plus dynamic imaging for physiologic extraction of the radiopharmaceutical from the blood pool into the liver parenchyma, excretion through the hepatic biliary system, localization to the gallbladder, and then post–Ensure Plus excretion from the gallbladder through the extrahepatic biliary system to the bowel. If there is a significant delay (>5–10 min) in extraction from the blood pool to the liver, it may be a sign of hepatic dysfunction, such as liver failure or acute hepatitis (Fig. 3) (*1*). Extraction to the liver but a lack of excretion to the biliary system may also suggest poor hepatic function or a high-grade biliary obstruction. As previously noted, if the gallbladder fails to fill, it may indicate a sign of acute cholecystitis versus cold bile or sludge obstructing entrance of the radiopharmaceutical. After assessment of the patient, one can consider rescheduling the hepatobiliary scintigraphy with sincalide pretreatment to ensure radiopharmaceutical localization to the gallbladder.

In pre– or post–Ensure Plus imaging, a delay in passage to the small bowel may suggest dysfunction of the sphincter of Oddi, characterized by a functional or anatomic obstruction (*41*,*42*). On hepatobiliary scintigraphy, the sphincter of Oddi manifests as decreased clearance of the radiopharmaceutical from the liver, dilation of the intra- and extrahepatic biliary ducts, and increased radiopharmaceutical concentration in the biliary system.

During excretion of the radiopharmaceutical from the biliary system into the small bowel, it is important to also assess for retrograde localization of the radiopharmaceutical to the stomach or esophagus (Fig. 4). This enterogastric reflux should be documented in the report, as it can result in an alkaline gastritis and may be a source of pain for the patient.

The most important step in evaluation and interpretation of Ensure Plus hepatobiliary scintigraphy for gallbladder ejection fraction is to report the gallbladder ejection fraction, which is normal if it is at least 33% (*8*). Rapid emptying of the gallbladder has also been reported and suggested as a possible cause of symptoms. Rapid emptying is reported as greater than 65%–80% (*43*). Case reports have reported that cholecystectomy in these cases of biliary colic can lead to symptomatic relief. Although a gallbladder ejection fraction is not the only determining factor for most surgeons, it can be a helpful quantitative measure in defining chronic functional gallbladder disorder in patients with biliary-type symptoms.

CONCLUSION

Determining the gallbladder ejection fraction is an important quantitative tool that assists surgeons in deciding whether a patient's biliary-type pain is due to chronic functional gallbladder disorder. Unfortunately, the primary cholecystagogue used to stimulate gallbladder contraction and sphincter of Oddi relaxation, sincalide, is often underproduced and faces chronic shortages. Consequently, nuclear medicine practitioners need to be aware of other effective oral cholecystagogues that can be used to determine

gallbladder ejection fractions. The best studied of these cholecystagogues is Ensure Plus, an affordable, palatable oral fatty meal that similarly induces gallbladder contraction and sphincter of Oddi relaxation for accurate gallbladder ejection fraction determination.

DISCLOSURE

The opinions and assertions expressed here are those of the authors and do not necessarily reflect the official policy or position of the Uniformed Services University or the Department of Defense. No potential conflict of interest relevant to this article was reported.

ACKNOWLEDGMENT

We thank Sofia C. Echelmeyer of Uniformed Services University of the Health Sciences for creating Figures 1A and B.

REFERENCES

1. Ziessman HA, O'Malley JP, Thrall JH. *Nuclear Medicine: The Requisites.* 4th ed. Elsevier; 2013:180–206.
2. Berk JE, Feigelson HH. Preliminary observations on the use of cholecystokinin in cholecystocholangiography and on simultaneous cholecystocholangiography and pyelography using Duografin. *Bull Sinai Hosp Detroit.* 1957;5:2.
3. Broden B. Experiments with cholecystokinin in cholecystography. *Acta Radiol.* 1958;49:25–30.
4. Torsoli A, Ramorino ML, Colagrande C, Demaio G. Experiments with cholecystokinin. *Acta Radiol.* 1961;55:193–206.
5. Shafer RB, Marlette JM, Morley JE. The effects of Lipomul, cholecystokinin, and TRH on gallbladder emptying. *Clin Nucl Med.* 1983;8:66–69.
6. Fink-Bennett D. Augmented cholescintigraphy: its role in detecting acute and chronic disorders of the hepatobiliary tree. *Semin Nucl Med.* 1991;21:128–139.
7. Watson A, Better N, Kalff V, Nottle P, Scelwyn M, Kelly MJ. Cholecystokinin (CCK)-HIDA scintigraphy in patients with suspected gall-bladder dysfunction. *Australas Radiol.* 1994;38:30–33.
8. Ziessman HA, Jones DA, Muenz LR, Agarval AK. Cholecystokinin cholescintigraphy: methodology and normal values using a lactose-free fatty-meal food supplement. *J Nucl Med.* 2003;44:1263–1266.
9. DiBaise JK, Richmond BK, Ziessman HH, et al. Cholecystokinin-cholescintigraphy in adults: consensus recommendations of an interdisciplinary panel. *Clin Gastroenterol Hepatol.* 2011;9:376–384.
10. Ziessman HA. Sincalide: A review of clinical utility, proper infusion methodology, and alternative cholecystogogues. *J Nucl Med Technol.* 2019;47:210–212.
11. Lam R, Zakko A, Petrov JC, Kumar P, Duffy AJ, Muniraj T. Gallbladder disorders: a comprehensive review. *Dis Mon.* 2021;67:101130.
12. Tulchinsky M, Ciak BW, Delbeke D, et al. SNM practice guideline for hepatobiliary scintigraphy 4.0. *J Nucl Med Technol.* 2010;38:210–218.
13. Westlake PJ, Hershfield NB, Kelly JK, et al. Chronic right upper quadrant pain without gallstones: does HIDA scan predict outcome after cholecystectomy? *Am J Gastroenterol.* 1990;85:986–990.
14. Ziessman HA. Functional hepatobiliary disease: chronic acalculous gallbladder and chronic acalculous biliary disease. *Semin Nucl Med.* 2006;36:119–132.
15. Preston JF, Diggs BS, Dolan JP, Gilbert EW, Schein M, Hunter JG. Biliary dyskinesia: a surgical disease rarely found outside the United States. *Am J Surg.* 2015; 209:799–803.
16. Krishnamurthy S, Krishnamurthy GT. Biliary dyskinesia: role of the sphincter of Oddi, gallbladder and cholecystokinin. *J Nucl Med.* 1997;38:1824–1830.
17. Clark CJ. An update on biliary dyskinesia. *Surg Clin North Am.* 2019;99:203–214.
18. Shaffer E. Acalculous biliary pain: new concepts for an old entity. *Dig Liver Dis.* 2003;35:20–22.
19. Yap L, Wycherley AG, Morphett AD, Toouli J. Acalculous biliary pain: cholecystectomy alleviates symptoms in patients with abnormal cholescintigraphy. *Gastroenterology.* 1991;101:786–793.
20. Christensen CT, Peacock JG, Vroman PJ, Banks KP. Scintigraphic findings beyond ejection fraction on hepatobiliary scintigraphy: are they correlated with chronic gallbladder disease? *Clin Nucl Med.* 2018;43:721–727.
21. Rosenbaum HD. Oral cholecystography. *JAMA.* 1974;230:672.
22. Feigelson HH, Edward Berk J, Joyrich MH, Gagliardi RA, Shufro AS. The effectiveness of oral cholecystagogues and intravenous cholecystokinin in producing bile duct visualization during oral cholecystography. *Radiology.* 1960;75:268–271.
23. Statman AJ. Experiences with a new oral cholecystagogue in preparation for cholangiography. *Am J Gastroenterol.* 1962;37:79–84.
24. Shopfner CE. Cholecystographic modifications to improve initial study opacification. *JAMA.* 1975;234:479–480.
25. Harvey IC. Milk chocolate as the fatty meal in oral cholecystography. *Clin Radiol.* 1977;28:635–636.
26. Hadigan C, Fishman SJ, Connolly LP, Treves ST, Nurko S. Stimulation with fatty meal (Lipomul) to assess gallbladder emptying in children with chronic acalculous cholecystitis. *J Pediatr Gastroenterol Nutr.* 2003;37:178–182.
27. Li AY, Yue H, Kavnoudias H, et al. Clinical utility of stimulated cholescintigraphy using a standardized Ensure-Plus fatty meal protocol in patients with suspected functional gallbladder disorder: a retrospective study of seven-years clinical experience. *ANZ J Surg.* 2022;92:774–780.
28. Peacock JG, Katchen JM, Christensen CT, Banks KP. Utilizing the cholecystagogue, Ensure Plus, results in similar hepatobiliary scintigraphy study results and patient outcomes status post cholecystectomy, in comparison with sincalide. *Clin Nucl Med.* 2020;45:1–6.
29. Fotos JS, Tulchinsky M. Oral cholecystagogue cholescintigraphy: a systematic review of fatty meal options. *Clin Nucl Med.* 2015;40:796–798.
30. Bobba VR, Krishnamurthy GT, Kingston E, Turner FE, Brown PH, Langrell K. Gallbladder dynamics induced by a fatty meal in normal subjects and patients with gallstones: concise communication. *J Nucl Med.* 1984;25:21–24.
31. Hopman WP, Rosenbusch G, Jansen JB, de Jong AJ, Lamers CB. Gallbladder contraction: effects of fatty meals and cholecystokinin. *Radiology.* 1985;157:37–39.
32. Mutirangura P, Siwawetkul W. Gallbladder contraction capacity in response to liquid fatty meal: a real time ultrasonographic study. *J Med Assoc Thai.* 1996;79:640–647.
33. Laufer I, Gledhill L. The value of the fatty meal in oral cholecystography. *Radiology.* 1975;114:525–527.
34. Brown PH, Krishnamurthy GT, Bobba VR, Kingston E, Turner FE. Radiation-dose calculation for five Tc-99m IDA hepatobiliary agents. *J Nucl Med.* 1982;23: 1025–1030.
35. Loberg MD, Cooper M, Harvey E, Callery P, Faith W. Development of new radiopharmaceuticals based on N-substitution of iminodiacetic acid. *J Nucl Med.* 1976; 17:633–638.
36. Ziessman HA. Hepatobiliary scintigraphy in 2014. *J Nucl Med Technol.* 2014;42: 249–259.
37. DiBaise JK, Richmond BK, Ziessman HA, et al. Cholecystokinin-cholescintigraphy in adults: consensus recommendations of an interdisciplinary panel. *Clin Nucl Med.* 2012;37:63–70.
38. LaFrance N. Alternatives to Kinevac: shortages lead to inventive measures. *J Nucl Med.* 2002;43(3):20N, 22N, 28N.
39. Bartel TB, Juweid ME, Ponto JA, Graham MM. Corn oil emulsion: a simple cholecystagogue for diagnosis of chronic acalculous cholecystitis. *J Nucl Med.* 2005;46:67–74.
40. Ensure® Plus nutrition shake. Abbott website. https://www.abbottnutrition.com/our-products/ensure-plus-nutrition-shake. Accessed November 14, 2023.
41. Afghani E, Lo SK, Covington PS, Cash BD, Pandol SJ. Sphincter of Oddi function and risk factors for dysfunction. *Front Nutr.* 2017;4:1.
42. Behar J, Corazziari E, Guelrud M, Hogan W, Sherman S, Toouli J. Functional gallbladder and sphincter of Oddi disorders. *Gastroenterology.* 2006;130:1498–1509.
43. Huckaby L, Timmapuri S, Prasad R. Biliary hyperkinesia: a potentially surgically correctable disorder in adolescents. *J Pediatr Surg Case Rep.* 2013;1:314–316.