Hepatobiliary Scintigraphy in 2014

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Cholescintigraphy with ^{99m}Tc-hepatobiliary radiopharmaceuticals has been an important, clinically useful diagnostic imaging study for almost 4 decades. It continues to be in much clinical demand; however, the indications, methodology, and interpretative criteria have evolved over the years. This review will emphasize state-of-the-art methodology and diagnostic criteria for various clinical indications, including acute cholecystitis, chronic acalculous gallbladder disease, high-grade and partial biliary obstruction, and the postcholecystectomy pain syndrome, including sphincter-of-Oddi dysfunction and biliary atresia. The review will also emphasize the use of diagnostic pharmacologic interventions, particularly sincalide.

Key Words: hepatobiliary scintigraphy; cholescintigraphy; acute cholecystitis; chronic cholecystitis; chronic acalculous gallbladder disease; biliary dyskinesia

Now almost 4 decades old, ^{99m}Tc cholescintigraphy continues to be a radionuclide imaging study in much clinical demand. Its strength lies in the fact that the diagnostic information provided defines pathophysiology rather than anatomy.

^{123}I- and ^{123}I-rose bengal were the first clinically useful cholescintigraphic agents; however, image quality was relatively poor (Fig. 1). ^{99m}Tc-hepatobiliary radiopharmaceuticals began to be widely used by the early 1980s.

The discovery of ^{99m}Tc-hepatobiliary (HIDA) radiopharmaceuticals was by chance. During investigation for a cardiac imaging radiopharmaceutical, it was found that ^{99m}Tc-labeled lidocaine was not a good cardiac imaging agent but cleared through the hepatobiliary system. With chemical modification, ^{99m}Tc-HIDA imaging agents were born. Loberg et al. reported on this in 1976 (*1*). Its structure is simply that of 2 lidocaine analogs bichelated to ^{99m}Tc by iminodiacetic acid (IDA) (Fig. 2). *HIDA* (hepatoiminodiacetic acid) has long been used as a generic term for cholescintigraphy.

Modifications of the benzene ring of the lidocaine analogs resulted in an alphabet soup of hepatobiliary radiopharmaceuticals (PIPIDA, BIDA, EIDA, DIDA, DISIDA, etc.), each with different rates of hepatic uptake and clearance. The first ^{99m}Tc-HIDA radiopharmaceutical was approved for clinical use by the Food and Drug Administration in 1982. Dimethyl IDA (lidofenin [Technescan; Mallinckrodt]) was a major advance, but image quality and diagnostic utility were suboptimal in patients with serum bilirubin levels above 5.0 mg/dL. It is no longer available.

In 1986, the Food and Drug Administration approved ^{99m}Tc-disofenin (diisopropyl-IDA [Hepatolite; Pharmalucence]). It provided images of diagnostic quality with bilirubin levels of as high as 25–30 mg/dL. In 1993, ^{99m}Tc-mebrofenin (bromotriethyl-IDA [Choletec; Bracco]) was approved. It had higher liver extraction (98% vs. 89%) and more rapid biliary clearance than ^{99m}Tc-disofenin (half-life of 19 min vs. 17 min).

After intravenous injection, ^{99m}Tc-HIDA radiopharmaceuticals are transported in the blood bound to serum albumin. They dissociate from albumin in the hepatic perisinusoidal space and are extracted by hepatocytes by receptor-mediated endocytosis, similar to bile salts, free fatty acids, and bilirubin. They then follow the same metabolic pathway as bilirubin, except that they are secreted into biliary caliculi unchanged, without undergoing conjugation.

This review will emphasize modern-day use and newer developments that affect clinical practice. Space does not permit review of all of the many clinical indications for cholescintigraphy (i.e., acute cholecystitis, chronic cholecystitis, acute biliary obstruction, partial biliary obstruction, sphincter-of-Oddi dysfunction, biliary atresia, biliary leak, biliary stent patency, enterogastric bile reflux, complications from the biliary diversion procedure, complications after liver transplantation, differential diagnosis of hepatic tumors, and prediction of remnant liver function after partial hepatectomy).

ACUTE CHOLECYSTITIS

Acute cholecystitis is the most common clinical indication for cholescintigraphy. Patients present with acute colicky pain in the right upper quadrant lasting hours or days. Except for low-grade fever and a moderately elevated leukocyte count, laboratory findings (including liver function studies) are usually normal. A
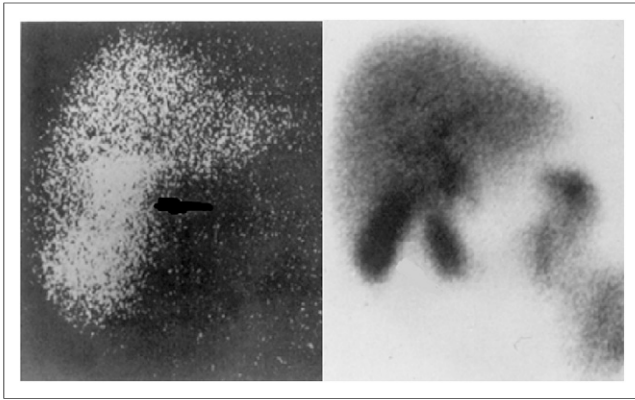
FIGURE 1. ^{123}I-rose bengal cholescintiscan (left) and ^{99m}Tc-HIDA cholescintiscan (right).

few patients will have an elevated level of serum bilirubin caused by stones lodged in both the cystic and the biliary ducts or, less commonly, by an impacted cystic-duct stone compressing the adjacent hepatic or common bile duct (Mirizzi syndrome).

A sequence of pathophysiologic events occurs with acute cholecystitis. Initially the cystic duct is obstructed, usually by a stone. The gallbladder mucosa becomes edematous, followed by neutrophilic infiltration, then mucosal ulceration, hemorrhage, and necrosis, and ultimately, if left untreated, the complications of perforation, gangrene, and abscess (2).

Ultrasonography

Ultrasonography is often part of the initial work-up for suspected hepatobiliary disease. It is readily available, does not use ionizing radiation, and can detect various intraabdominal diseases in addition to acute cholecystitis, such as biliary obstruction, pancreatitis, and tumors.

The sonographic findings of acute cholecystitis are usually nonspecific and secondary pathologic findings. Gallstones are present in most patients with acute cholecystitis; however, because cholelithiasis is common in the general population and often remains asymptomatic for a lifetime, its presence is not diagnostic, except that the lack of gallstones makes a nonbiliary process more likely.

The sonographic findings of gallbladder wall thickening, dilatation, pericholecystic fluid, and sludge are nonspecific. Intramural sonolucency, due to edema, and the sonographic Murphy sign are more specific, but the former does not have high sensitivity and the latter is observer-dependent and can be unreliable. The more of these findings that are present, the greater the likelihood will be that the diagnosis is acute cholecystitis (3). However, the ultrasonographic criteria used to diagnose acute cholecystitis vary.

Accuracy of Cholescintigraphy and Ultrasonography

A problem with reading the published literature about the relative accuracy of ultrasonography and cholescintigraphy to diagnose acute cholecystitis is the different histopathologic criteria that have been used (4). Strict criteria for acute cholecystitis require leukocyte infiltration and hemorrhagic necrosis. More liberal criteria would include edema. This inconsistency is most problematic when only a single diagnostic imaging technique is investigated. The accuracy of a test is most reliable when there is a direct comparison of two or more imaging methods using the same histopathologic criteria in the same patient population.

Although several published investigations have reported high accuracy for ultrasonography to confirm the diagnosis of acute cholecystitis, only a few have directly compared the relative accuracy of sonography and cholescintigraphy in the same investigation. Six of 7 direct-comparison published investigations have shown superior accuracy for cholescintigraphy over sonography (Table 1) (5–11). CT and MR are most useful for detection of suspected complications.

[Table 1]

Cholescintigraphy demonstrates the primary underlying pathophysiology of acute cholecystitis, that is, obstruction of the cystic duct, and thus the ^{99m}Tc-HIDA radiopharmaceutical cannot enter the gallbladder. Stones are the cause of obstruction in more than 90% of patients, but stones are rarely visualized by anatomic imaging because of their small size and the sonographic acoustic problems in the small cystic duct.

Patient Preparation

Patients should ingest nothing by mouth for 3–4 h before injection of the ^{99m}Tc-HIDA radiopharmaceutical. This interval allows time for the ingested meal to have passed though the proximal small bowel, where fat stimulates endogenous cholecystokinin release and thus gallbladder contraction, and then time for the gallbladder to relax. When patients are interviewed about when they last ate, a question on what they ate is helpful. A meal with at least 10 g of fat is required to contract and empty the gallbladder.

Patients who have been fasting for more than 24 h have had no stimulation to contract the gallbladder and will likely have concentrated viscous jellylike bile that can prevent entry of radiotracer and result in a false-positive study for acute cholecystitis. In these patients, sincalide (Kinevac; Bracco) should be administered before the study to empty the gallbladder. The pharmacologic dose (0.02 μg/kg) should be infused over 60 min, similar to what is described later in this review for optimal gallbladder contraction. However, some patients with chronic cholecystitis may have poorly contracting gallbladders and thus not respond to the sincalide, resulting in a false-positive study. The ^{99m}Tc-HIDA agent should be injected at least 30 min later to provide sufficient time for gallbladder relaxation.

Scintigraphic Protocol

The imaging protocol for cholescintigraphy has become fairly standardized (12). A 60-s blood flow phase (1- to 3-s frames) is optional. The diagnostic yield is not high; however, increased flow to the region of the gallbladder fossa can be seen in severe cases of acute cholecystitis and in other causes of abdominal pain, such as
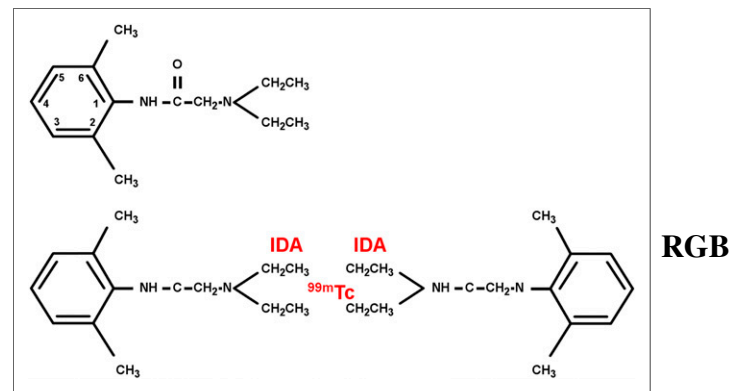

RGB

FIGURE 2. Chemistry of ^{99m}Tc-HIDA radiopharmaceuticals: lidocaine (A) and ^{99m}Tc-mebrofenin (B). Two lidocaine analogs are bichelated to ^{99m}Tc by IDA.

TABLE 1
Accuracy of Ultrasonography vs. Cholescintigraphy for Acute Cholecystitis: Direct-Comparison Investigation

Publication	Year	No. of patients	Cholescintigraphy		Ultrasonography	
			Sensitivity	Specificity	Sensitivity	Specificity
Stadalnik et al. (5)	1978	120	87	100	70	93
Zeman et al. (11)	1981	200	98	81	67	82
Worthen et al. (8)	1981	113	95	100	76	100
Ralls et al. (10)	1982	59	86	84	86	90
Freitas et al. (6)	1982	195	98	90	81	60
Samuels et al. (7)	1983	194	97	93	97	64
Chatziioannou et al. (9)	2000	107	92	89	40	89

intraabdominal infection or a vascular tumor. After the flow study, 1-min dynamic images are acquired for the remaining 59 min.

In the setting of good hepatic function and biliary clearance, nonfilling of the gallbladder is diagnostic of acute cholecystitis but must persist on delayed images for up to 4 h (13) or for 30 min after morphine infusion (14).

Gallbladder filling after 1 h with normal biliary-to-bowel transit is usually due to chronic cholecystitis (15). The presence of intestinal transit before gallbladder filling during the first hour of imaging is also suggestive of chronic cholecystitis (16). Delayed gallbladder filling is caused by a functional resistance to flow through the cystic duct, often due to viscous concentrated bile within the gallbladder, gallstones, chronic mucosal thickening, and fibrosis. Visualization of the gallbladder by the end of the first hour after these patients are pretreated with cholecystokinin is considered evidence for a functional mechanism (17). Other scintigraphic findings suggestive of chronic cholecystitis include delayed biliary-to-bowel transit with normal gallbladder filling (18).

The most common cause for a false-positive finding of acute cholecystis is chronic cholecystitis. Therefore, the prevalence of chronic cholecystitis in the population under study affects the overall specificity of the test. However, most patients with chronic cholecystitis have gallbladder filling by 1 h.

The use of morphine sulfate (MS) is often preferred over the delayed imaging method for confirmation of the diagnosis of acute cholecystitis because a shorter time is required and the problem of rapid ^{99m}Tc-mebrofenin liver clearance is reduced (19). An additional 74–111 MBq (2–3 mCi) of ^{99m}Tc-mebrofenin are often administered at the time of morphine infusion if there has been substantial liver clearance. This procedure, although it would probably be useful, has not been standard for the delayed imaging method. The MS method is at least as accurate as and perhaps more accurate than the delayed imaging method (20).

Subanalgesic doses of intravenous MS contract the sphincter of Oddi and increase intrabiliary pressure, causing preferential flow through the cystic duct if it is patent. A weight-based dose of MS is recommended, 0.04 mg/kg (20). Enterogastric reflux is not uncommon, probably because of relaxation of the pyloric sphincter. Levorphanol or meperidine (Demerol; Abbott Laboratories) could theoretically be used if MS is unavailable, but there are few published data to confirm its accuracy (21).

MS is usually administered 60 min after ^{99m}Tc-HIDA injection. Earlier infusion, such as at 30 min, has been successfully used, but one loses the ability to differentiate chronic from acute cholecystitis (22). MS should not be given unless there is good biliary duct clearance and biliary-to-bowel transit; otherwise, post-MS differentiation of a pathologic partial biliary obstruction from an MS

pharmacologic effect may not be possible. There is no contraindication to MS administration, except for a past allergic reaction. MS is not useful in patients who do not have a functioning sphincter of Oddi (e.g., patients with a common duct stent or sphincterotomy). Like the delayed imaging method, there is likely to be preferential biliary duct drainage that could result in a false-positive finding of acute cholecystitis (23).

False-Positive Findings of Acute Cholecystitis

Although the sensitivity of ^{99m}Tc-HIDA radiopharmaceutical for the diagnosis of acute cholecystitis is high (95%–98%) and the specificity quite good (90%), rare false-negative and somewhat more common false-positive findings occur (15). Patients who do not follow nothing-by-mouth instructions is one reason for a false-positive finding, and patients who have been fasting or receiving hyperalimentation for greater than 24 h is another. A severe concurrent illness is an important cause for false-positive findings (24,25), reducing the specificity of the test to about 70%. Patients with poor hepatocellular function may have a false-positive finding because of altered tracer pharmacokinetics, that is, slower uptake and clearance. Thus, the time required for visualization of the gallbladder and biliary-to-bowel transit is prolonged, and the usual diagnostic time intervals do not apply. Delayed imaging is often required, up to 24 h.

Cystic Duct Sign

The cystic duct sign must not be misinterpreted as gallbladder filling (26). It is caused by dilation of the cystic duct secondary to distal cystic duct obstruction. However, the radiotracer is seen somewhat medial to the gallbladder fossa as a focus that is smaller than expected for gallbladder filling. Misinterpretation as gallbladder filling can have serious patient-treatment consequences. SPECT/CT can help confirm the diagnosis (Fig. 3) (27). [Fig. 3]

During cholescintigraphy that has been ordered to confirm or exclude acute cholecystitis, acute or partial obstruction of the common bile duct may be seen instead. Symptoms of the two entities can be similar, and as many as 70% of these patients do not have biliary dilatation on ultrasonography (28).

Rim Sign

The rim sign, that is, increased uptake of the ^{99m}Tc-HIDA agent in the liver adjacent to the gallbladder fossa, is a useful ancillary finding seen in about 25%–35% of patients with acute cholecystitis (29–31). This scintigraphic finding is seen in patients in the later stages of the histopathologic spectrum of the disease, that is, with gallbladder hemorrhage, necrosis, and ulceration (29), and has been associated with an increased incidence of gangrene and perforation (30). Although not sensitive for the diagnosis of acute
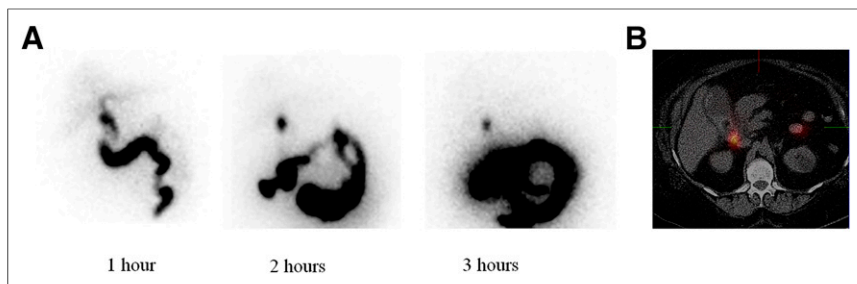
FIGURE 3. Cystic duct sign. (A) ^{99m}Tc-HIDA scan ordered to rule out acute cholecystitis. Images show focal accumulation of activity medial to usual position of gallbladder, which remains mostly unchanged over time. (B) Ten-minute SPECT/CT image in same patient shows that focal activity is in cystic duct just distal to occluding cystic duct stone. (Reprinted with permission of (27).)

cholecystitis, it is very specific. The rim sign is caused by severe gallbladder inflammation extending to adjacent liver, resulting in increased blood flow to that area, increased delivery of the radio-tracer to that region of the liver, and thus increased uptake. In some patients, surgeons have described fibrinous inflammatory adhesions that can make it difficult to remove the gallbladder from the adjacent liver.

Acalculous Form of Acute Cholecystitis

Acalculous acute cholecystitis occurs in less than 10% of patients with acute cholecystitis. No stones are present in the gallbladder or cystic duct. This entity typically occurs in patients who have had multiple traumatic injuries, extensive serious burns, postoperative complications, shock, sepsis, or other serious illnesses. Acalculous acute cholecystitis is associated with a high morbidity and mortality, at least partly because the disease presents atypically and may be obscured by the primary illness.

Most patients with acute acalculous cholecystitis have cystic duct obstruction not caused by a stone. In some cases, the obstruction is due to kinking, fibrosis, adhesive bands, anomalous vessels, tumor, or lymphadenopathy. In most cases the cause is inspissated bile, cellular debris, and local edema. In most of these patients, the diagnosis can be made with cholescintigraphy. However, perhaps a quarter of patients with acute acalculous cholecystitis do not have cystic duct obstruction but rather direct inflammation of the gallbladder wall secondary to sepsis, toxemia, or ischemia. Because there is no cystic duct obstruction, the gallbladder may visualize on ^{99m}Tc cholescintigraphy, resulting in a false-negative finding for acute cholecystitis. The diagnostic sensitivity of cholescintigraphy varies in the literature, and patient numbers are small; however, it is probably in the range of 70%–80%, compared with more than 95% for acute calculous cholecystitis (27).

In patients with a clinically suspected false-negative finding of acute acalculous cholecystitis, the diagnosis can sometimes still be made. If present, the rim sign will confirm the diagnosis with a high degree of certainty. In others, sincalide can be helpful. Diseased gallbladders, acute or chronic, do not contract well. Normal gallbladder contraction rules out acute or chronic cholecystitis. However, poor gallbladder contraction will not allow differentiation between acute and chronic gallbladder disease.

Although patients with acute acalculous cholecystitis are sick and need surgical intervention, surgeons are often hesitant to operate on them without a firm diagnosis because of the high surgical risk. In these cases, radiolabeled leukocytes can be useful. ^{111}In-labeled leukocytes have the advantage of having no hepato-biliary clearance (32). Images should be acquired early, at 4 h, and

if necessary at 24 h. However, good results have been reported with ^{99m}Tc-hexame-thylpropyleneamine oxime leukocytes, despite clearance of the radiopharmaceutical through the hepatobiliary system (33). Imaging should be performed by 2 h, before hepatobiliary clearance occurs.

CHRONIC GALLBLADDER DISEASE

Patients with chronic calculous chole-cystitis present clinically with symptoms of recurrent biliary colic. Their physician often orders ultrasonography to confirm the diagnosis. Cholelithiasis is detected, and the patient is referred for cholecystec-tomy. These patients rarely have cholescintigraphy. On occasion, a referring physician suspects that the patient's abdominal pain may not be caused by the stones in the gallbladder and will request a radionuclide study of gallbladder ejection fraction (GBEF). Gall-stones are common, but fewer than 15% of patients with gallstones followed for 20 y developed biliary colic (34). A normal GBEF makes symptomatic chronic cholecystitis unlikely, confirming the clinician's suspicion that the patient has asymptomatic cholelithiasis and that another cause for the pain must be sought (35). There is no contraindication to sincalide infusion in patients with cholelithiasis.

Most patients referred for sincalide cholescintigraphy with GBEF are suspected to have chronic acalculous cholecystitis (CAGBD). Ultrasonography did not show stones. The acalculous form of the disease is reported to occur in approximately 5%–10% of patients with a final histopathologic diagnosis of chronic cho-lecystitis (34); however, recent laparoscopic studies suggest the frequency may be higher, perhaps 25% (36).

Many different names have been used for suspected cases of CAGBD, including cystic duct syndrome, gallbladder spasm, gall-bladder dyskinesia, and functional gallbladder disease. These patients have recurrent biliary colic and poor gallbladder contrac-tion, are cured by cholecystectomy, and usually have gallbladder histopathologic findings of lymphocyte infiltration and fibrosis similar to gallbladders with the calculous form of the disease but without stones. Patients with asymptomatic cholelithiasis do not have inflammatory changes of the gallbladder.

Publications Confirming the Diagnostic Utility of GBEF

Early studies published in the 1970s, using oral cholecystog-raphy and cholecystokinin or a fatty meal to stimulate gallbladder contraction, reported that the gallbladders of many patients with CAGBD contract poorly. However, published investigations reported conflicting results on whether this was a dependable diagnostic finding (37,38). The methodology varied, interpretation was sub-jective, and cholecystokinin was often given as a bolus, a problem discussed below. When ^{99m}Tc-HIDA radiopharmaceuticals be-came available, many investigators were quick to realize that this question might be answered with quantitative cholecystokinin cholescintigraphy (39).

The first published investigation, reported by Topper et al. in 1980, found that GBEF was predictive of CAGBD and a good clinical response to cholecystectomy (40). By the early 1990s, at least 22 publications reported similar results. However, all but one were retrospective.

One of the largest retrospective studies was by Fink-Bennett, et al. published in 1991 in *The Journal of Nuclear Medicine* (41).

They studied 374 patients referred for suspected CAGBD. Of 113 patients with a low GBEF who subsequently underwent cholecystectomy, 97% had relief of their symptoms and 94% had histopathologic evidence of chronic cholecystitis. They infused sincalide, 0.02 μg/kg, over 3 min and defined an abnormal GBEF as less than 35%, for uncertain reasons. They had studied a group of asymptomatic healthy subjects, but only 9 had a GBEF greater than 35%. The investigators certainly did not use these data to establish their reference values. However, as a result of this study with seemingly good results, many imaging clinics followed the authors' sincalide infusion protocol and reference values.

The methodology varied considerably among the retrospective investigations, which used different forms of cholecystokinin, different total doses administered (0.01–0.04 μg/kg), different infusion lengths (bolus, 1–3 min, 15 min, 20 min, and 30–45 min), and different reference values (42). None of these studies established reference values based on the methodology they used. Curiously, 6 published retrospective investigations did not find that GBEF was predictive of CAGBD and good response to cholecystectomy (42).

The only prospective and randomized study was reported by Yap et al. It was published in the same month and year as the publication of Fink-Bennett et al. (41) but in the gastroenterology literature and thus was not familiar to most of the nuclear medicine community (43). This prospective study randomized—to surgical or nonsurgical therapy—patients referred with suspected CAGBD who had a low GBEF. They used a very different sincalide infusion method, 0.02 μg/kg/h infused over 45 min, with imaging and quantification at 60 min. Importantly, they established their own reference values based on 30 healthy subjects. An abnormal GBEF was found to be less than 40%.

In this prospective randomized study, 92% (10/11) of the patients with a low GBEF had resolution of their symptoms after cholecystectomy and had histopathologic evidence of chronic cholecystitis. Patients randomized to the nonsurgical arm continued to have pain, some severe enough to demand surgery, and they also had resolution of their symptoms after cholecystectomy. This is considered to be an excellent investigation, with the main limitation being that the number of subjects, 21, was not high.

Reference Values for GBEF

Cholecystokinin is a 33- to 58-amino-acid polypeptide hormone. The terminal octapeptide is the physiologically active form of the hormone. Sincalide is an analog of the terminal octapeptide. Kinevac is the only commercially available Food and Drug Administration–approved parenteral cholecystagogue. The only contraindication to sincalide is a history of a previous allergic reaction (quite rare) and pregnancy.

GBEF reference values after sincalide infusion vary with the dose administered and the infusion time. As early as 1985, there was evidence that methodology mattered. One study of 31 healthy subjects who received 1- to 2-min infusions of 0.015 μg/kg found that GBEFs varied between 7% and 85% (44). In another study, Sarva et al. studied 2 different groups of subjects, one with a 1-min infusion of sincalide, 0.02 μg/kg, and another with a 45-min infusion (45). The results showed higher GBEFs (mean, 77% vs. 52%) and a considerably narrower range of response (65%–96% vs. 12%–92%) with the 45-min infusion than with the 1-min infusion. These were not truly healthy subjects but rather symptomatic patients who were referred for cholescintigraphy but turned out to have nonbiliary causes for their pain. Both studies suggested considerable GBEF variability with short infusions in healthy subjects.

Two subsequent investigations studied proven healthy subjects with 2 different sincalide infusion methods on different days. Those who had a 3-min infusion of 0.01 or 0.02 μg/kg had extreme variability in GBEF (0%–100%), and clinically useful reference values could be established (46,47). False-positive results, that is, a low GBEF with a 3-min infusion but a normal GBEF with a 30- or 60-min infusion in the same subjects, occurred in a third of subjects. Sincalide infusions of 30 min and 60 min in the same subjects showed much less variability, and reference GBEF values could be determined (>30% and >40%, respectively).

In the same studies, it was shown that a 3-min infusion of sincalide (0.37 or 0.74 kBq [0.01 or 0.02 μCi]/kg) caused abdominal cramping or nausea in 50% of healthy subjects (46,47). Those same subjects did not have pain with 30- or 60-min sincalide infusions. Even 15-min infusions may cause abdominal symptoms in some subjects (48).

In the 1960s and 1970s, it was reported that a bolus infusion of cholecystokinin can result in spasm of the cystic duct and gallbladder neck, resulting in ineffective gallbladder contraction (49,50). The described data suggest that the reason for the variable and often poor response to short infusions of sincalide may be caused by gallbladder sensitivity to the rapid nonphysiologic infusion of sincalide, causing a spasm of the cystic duct and gallbladder neck similar to that seen with bolus infusions (51).

It has been said often and wrongly that pain during sincalide infusion is diagnostic of chronic cholecystitis, because it reproduces the patient's pain. Although investigations have shown that this is not true, the erroneous idea persists (52). Pain seen with sincalide is dependent on dose rate and is unrelated to the presence of underlying disease. Slower infusions are a more physiologic infusion method, mimicking endogenous secretion of cholecystokinin in response to eating a fatty meal, and almost never result in nausea or abdominal discomfort (51).

A multicenter investigation was designed to determine the optimal methodology for sincalide infusion. The study was sponsored by the commercial distributor of Kinevac, Bracco Diagnostics, Inc., which provided an unrestricted grant to the Gastrointestinal Council of the Society of Nuclear Medicine (now morphed to the General Clinical Nuclear Medicine Council of the Society of Nuclear Medicine and Molecular Imaging). Bracco had no input into the study design, analysis of results, or conclusions. The study directly compared 15-, 30-, and 60-min sincalide infusions (0.02 μg/kg) in 60 healthy subjects, 15 each at 4 different institutions (48). The 3 different sincalide infusion studies were performed at 2–3 d apart. The purpose of the investigation was to determine which methodology showed the least variability in subject response and to establish reference values. The investigation found that the 60-min infusion method had the least variability (percentage coefficient of variance) and the narrowest range for GBEF reference values (Fig. 4). [Fig. 4] The lower range of normal was 38%, similar to the prospective study of Yap et al. (<40%) using a similar but not identical protocol (43).

An expert panel of gastroenterologists, surgeons, and nuclear medicine physicians subsequently met and published a consensus report in both the gastroenterology literature and the nuclear medicine literature (53,54). The panel recommended that the 60-min method for infusing sincalide described in the multicenter trial should become the standard, specifically, 0.02 μg/kg infused at a constant rate via an infusion pump or slow drip over 60 min, with imaging and quantification over the entire 60-min period. Some gastroenterologists think there are insufficient evidence-based data
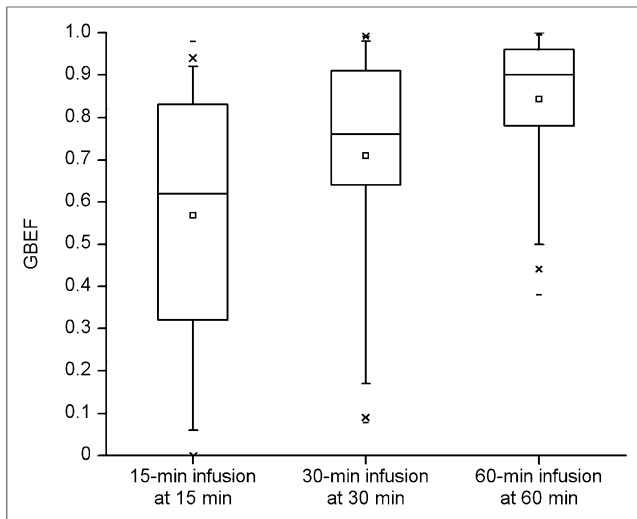
FIGURE 4. Comparison trial of multicenter sincalide infusion method. Box plots show distribution of GBEF values for 3 different infusion groups for different lengths of infusion time. The 60-min infusion had the highest GBEFs and the lowest variability. Boxes represent interquartile range (25th–75th percentiles, median line in center, mean is square), bars represent fifth and 95th percentiles, ×s represent first and 95th percentiles, and dash is minimum and maximum. (Reprinted with permission of (*48*).)

on the utility of the GBEF study (*55*). The panel therefore also recommended that a large prospective and randomized multicenter trial be initiated to confirm that a radionuclide GBEF study can diagnose CAGBD and predict a good response to cholecystectomy, using the panel's recommended infusion method (*56*).

Reference values are not necessarily the same thing as determination of a GBEF cutoff value that best predicts CAGBD and response to cholecystectomy based on the results of a large prospective study. However, until that study is done, we must use established reference values. Using the standardized methodology, borderline GBEF values below 38% should be interpreted with caution. The lower the GBEF, the more confident one can be of the diagnosis.

A GBEF study should be performed on an outpatient basis (*57*). Acute illness other than gallbladder disease in hospitalized patients can potentially result in a low GBEF. Importantly, many inpatients are taking medications during hospitalization that can inhibit gallbladder contraction (*22*). These include opiate drugs, atropine, benzodiazepine, ethanol, octreotide, nicotine, nifedipine, pirenzepine, progesterone, and theophylline. In some cases, referring physicians insist. In this situation, a normal GBEF result rules out disease. An abnormal GBEF result should be confirmed on an outpatient basis.

Morphine has a 4- to 6-h half-life and can inhibit sincalide-stimulated gallbladder contraction. Regardless, in approximately 50% of patients who receive sincalide subsequent to having been administered morphine during cholescintigraphy, the gallbladder contracts normally (*58*). Again, a normal GBEF result rules out acute cholecystitis or symptomatic chronic gallbladder disease, but a low GBEF is nondiagnostic in this clinical setting (*57*).

Unavailability of Sincalide

In 2002 and again this past year, Kinevac was not commercially available because of unspecified production problems (*59*). Pharmacy-compounded sincalide, produced under state authorization and regulated under the practice of pharmacy, has been used in these circumstances, with some reported success (*60*). However, concern has been expressed by radiopharmacists that the quality control required for this polypeptide hormone is considerably greater than for many other radiopharmaceuticals that have also been out of production at times, such as dimercaptosuccinic acid and macroaggregated albumin (*61*). The quality control testing required for sincalide may be beyond the capabilities of some compounding pharmacies and thus may not be performed—for example, testing of the sincalide contractile property using guinea pig gallbladders. The radiopharmacists concluded that using pharmacy-compounded sincalide puts at risk the diagnosis and the physician prescribing the drug.

At least 3 oral cholecystagogues have been studied and reference values established. These include whole milk (300 mL) (*62,63*), lactose-free EnsurePlus (237 mL [8-oz]; Abbott Laboratories) (*64*), and Lipomul (a soybean oil emulsion) (30 mL) (*65*). After ingestion, images are acquired for 1 h. The lower range of reference values reported for the GBEFs are 51%, 33%, and 20%, respectively. Reference normal values depend on the amount of fat and protein in the administered meal.

BILIARY OBSTRUCTION

High-Grade

High-grade biliary obstruction is a surgical emergency. There are 2 types—that caused by tumor and that caused by cholelithiasis. Patients with obstruction caused by tumor, for example, pancreatic cancer, present with painless hyperbilirubinemia. Anatomic imaging will detect dilated biliary ducts and often the tumor causing the obstruction.

Obstruction caused by cholelithiasis presents differently, that is, as acute severe biliary colic. The obstruction causes an increase in intrabiliary duct pressure. Bile flow is reduced, followed by ductal dilatation. However, dilatation of biliary ducts may not be seen on anatomic imaging until 24–72 h after the obstructive event. Thus, ultrasonography findings may be negative when a patient presents in the emergency room with acute pain. It is in these patients that cholescintigraphy can play an important diagnostic role, because the pathophysiologic scintigraphic findings are seen promptly after the obstructive event.

The classic scintigraphic picture of acute high-grade biliary obstruction demonstrates good hepatic uptake and function (rapid blood pool clearance) but no biliary secretion, because of the high intrabiliary back-pressure. Delayed images, even up to 24 h, often show only a persistent hepatogram. With lower degrees of high-grade obstruction, tracer may, over time, enter biliary ducts, but this will be delayed and without biliary-to-bowel transit. If the patient has good hepatic function, high-grade biliary obstruction can often be diagnosed within the first hour of imaging after injection of the ^{99m}Tc-HIDA radiopharmaceutical. The referring physician should be promptly notified.

With reduced hepatic function, delayed imaging may be required to differentiate biliary obstruction from primary hepatic dysfunction. If biliary obstruction is more chronic, secondary hepatic dysfunction can result and the diagnosis can be uncertain because of the overlap of findings. However, the two can usually be differentiated. Delayed transit to the bowel without retention in the biliary ducts is diagnostic of hepatic dysfunction rather than obstruction.

In patients who have had prior biliary obstruction, the biliary ducts often remain dilated, even with appropriate curative therapy. If these patients present again with abdominal pain, the persistently dilated ducts are not diagnostic of obstruction. Physiologic imaging with cholescintigraphy is required to determine whether

bile clearance is normal (not obstructed) or delayed (obstructed) (*15,66*).

Partial

Partial obstruction presents differently from high-grade obstruction. Patients complain of recurrent biliary colic. Liver function test results are normal. The bile ducts are not dilated. Cholescintigraphic images demonstrate good hepatic uptake, prompt secretion into the biliary ducts, and filling of the gallbladder; however, clearance from the biliary ducts is delayed, best seen in the common hepatic or common bile duct, depending on the site of obstruction. Biliary-to-bowel transit does not exclude partial biliary obstruction. Poor clearance from biliary ducts is diagnostic.

Cholescintigraphy has been found superior to ultrasonography for the diagnosis of partial biliary obstruction (*66*), with a 98% sensitivity for ^{99m}Tc-HIDA scintigraphy versus 78% for ultrasonography, and similar specificities of 85%–86%. MR cholangiopancreatography is often performed for suspected biliary obstruction. This imaging methodology does well at demonstrating dilated ducts, large stones, and tumors but not so well at detecting small obstructing stones.

Delayed biliary duct clearance and biliary-to-bowel transit with normal hepatic function can have causes other than partial obstruction. Biliary duct retention and delayed biliary-to-bowel transit at 60 min is seen in up to 20% of healthy subjects, supposedly due to a hypertonic sphincter of Oddi (*67*). A functional delay in biliary-to-bowel transit also occurs in up to 50% of patients who are administered sincalide to empty the gallbladder before cholescintigraphy (*68*). As the gallbladder relaxes after contraction, a negative pressure within it relative to the biliary ducts results in preferential flow via the cystic duct to the gallbladder rather than through the common duct and into the intestines. Delayed biliary-to-bowel transit is also seen in patients with chronic cholecystitis (*13*). The reason is uncertain but may be due to an ampullitis caused by recurrent passage of small stones. Pancreatitis has also been associated with delayed transit.

These functional causes of delayed biliary transit can be differentiated from biliary obstruction either by obtaining delayed images or by infusing sincalide. The short half-life of sincalide in the blood (2.5 min) allows for repeated infusion in patients pretreated with sincalide because they have fasted for more than 24 h (*69*). In patients with a functional cause for delayed transit, prompt biliary-to-bowel transit will result from sincalide infusion as the sphincter of Oddi relaxes. If clearance is poor, obstruction must be considered. Sincalide should be infused using the 60-min infusion methodology described above for stimulating gallbladder contraction. Cholelithiasis is not a contraindication to the administration of sincalide.

POSTCHOLECYSTECTOMY PAIN SYNDROME

The postcholecystectomy pain syndrome refers to the subsequent development of recurrent episodes of abdominal pain in patients who have had cholecystectomy for symptomatic chronic cholecystitis. This syndrome occurs in 10%–20% of postcholecystectomy patients (*70*). Hepatobiliary causes for the recurrent pain include retained and recurrent stones, biliary stricture, tumors, a cystic duct remnant, and obstruction of the sphincter of Oddi. The explanation for presentation after cholecystectomy is that the biliary system no longer has a pressure-release mechanism, formerly served by the gallbladder. Increased pressure produces the pain.

Sphincter-of-Oddi Dysfunction

Sphincter-of-Oddi dysfunction is a poorly understood clinical entity that presents weeks, months, or years after cholecystectomy

as either recurrent episodic biliary colic pain (stage I), recurrent pain associated with elevated liver enzymes or dilated ducts (stage II), or episodic pain with elevated liver enzymes and dilated biliary ducts (stage III) (*71*). The cause is a partial biliary obstruction at the level of the sphincter of Oddi, not caused by stones, stricture, or tumor. Two types have been described, stenosis (fixed) and dyskinesia (reversible). Sphincter dysfunction cannot be diagnosed before cholecystectomy (*72*). Histopathologic findings are often normal, although some patients have inflammation, muscular hypertrophy, fibrosis, or adenomyosis in the papillary zone.

All biliary causes for the postcholecystectomy pain syndrome have a similar scintigraphic pattern on cholescintigraphy, that of a partial biliary obstruction. Qualitative image analysis is often adequate to make the diagnosis (*73*). Scintigraphy shows prompt hepatic uptake and secretion into the biliary ducts but poor ductal clearance—best visualized in the common duct—seen at 1 h after injection of the ^{99m}Tc-HIDA radiopharmaceutical. At 2 h no further ductal clearance occurs or retention may be greater than at 1 h.

Quantitative methods have been investigated to diagnose sphincter-of-Oddi dysfunction (*74,75*). Published reports vary in the selected regions of interest and the quantitative parameters used. One published method originally developed at Johns Hopkins University and still routinely used calls for an initial infusion of sincalide, 0.02 μg/kg over 3 min, with the infusion completed 15 min before ^{99m}Tc-HIDA injection (*75*). The infusion was lengthened to 10 min over a decade ago, probably because of concern about reports that short infusions are disadvantageous for gallbladder contraction. The study is acquired for 60 min. The purpose of sincalide infusion is to increase bile flow and thus stress a partially obstructed sphincter, similar to what is done with furosemide renography for suspected renal obstruction. A longer infusion, as recommended for gallbladder contraction, is not used for this indication because its effect would be to relax the sphincter of Oddi, which would be counterproductive to trying to stress the sphincter. Whether the infusion is 3 or 10 min is probably inconsequential and may even be homeopathic regarding the results because of its short half-life in serum of 2.5 min.

A semiquantitative score is primarily calculated on the basis of image analysis, for example, time of first biliary secretion, percentage of common duct emptying, and time of initial biliary-to-bowel transit. Common duct and liver time–activity curves are generated as ancillary information (*75*). If the summed score is negative, attention is directed to nonbiliary causes. If positive, endoscopic retrograde cholangiopancreatography (ERCP) is performed to rule out stones, stricture, or tumor. If none of these is found, sphincter-of-Oddi dysfunction is assumed and sphincterotomy often follows.

Enthusiasm for ^{99m}Tc cholescintigraphy for sphincter-of-Oddi dysfunction has ebbed at some centers because of publications suggesting poor accuracy. One investigation compared 2 different quantitative methods, including the one described above. Elevated basal sphincter pressure detected on sphincter-of-Oddi manometry was the gold standard. The investigation showed that both radionuclide quantitative techniques were inferior to manometry (*76*). There have been criticisms of the investigation, one of these being that the authors used protocols different from the initially described methods—for example, a 60-min infusion of sincalide rather than 3 or 10 min. Importantly, manometry is seldom used anymore because of the frequent occurrence of serious side effects, particularly pancreatitis.

An independent gold standard superior to manometry would be patient outcome; however, few published data are available. A study
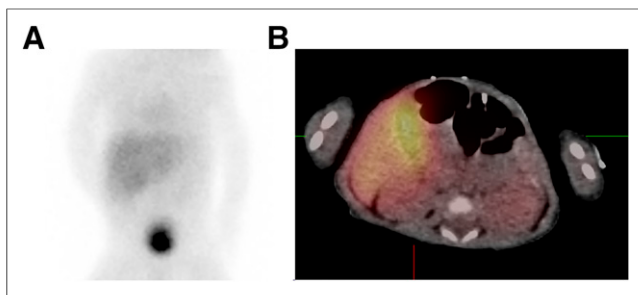
FIGURE 5. Study ordered to confirm or exclude biliary atresia. (A) Six-hour ^{99m}Tc-HIDA planar static image shows equivocal gallbladder filling and biliary-to-bowel transit. (B) Ten-minute SPECT/CT acquisition confirms activity in gallbladder, excluding biliary atresia. (Reprinted with permission of (*27*).)

subsequent to the ones described above comparing scintigraphy with manometry showed that although scintigraphy was less sensitive, it successfully predicted outcome after sphincterotomy in 93% of patients, compared with 57% with manometry (*77*).

Many centers perform ERCP if the diagnosis is clinically suspected, in order to rule out stones, stricture, and tumor. Once these have been ruled out, a sphincterotomy is performed. However, ERCP by itself is also associated with serious side effects. Other therapies have been investigated, such as drugs, Botox (onabotulinumtoxinA; Allergan Inc.), and stents, but data are limited or inconclusive and further studies are needed. It is my opinion and that of my referring physicians that quantitative cholescintigraphy can be a valuable screening tool for partial biliary obstruction and sphincter-of-Oddi dysfunction. If the results are negative, a nonbiliary cause should be sought. If positive, further biliary investigation is indicated, for example, ERCP.

Biliary Atresia

Biliary atresia presents as neonatal cholestatic jaundice. It is caused by a progressive inflammatory sclerosis that obliterates extrahepatic and intrahepatic biliary ducts. Early diagnosis is critical and must be made within the first 60 d of life to prevent irreversible liver failure. Treatment requires a palliative hepato-portoenterostomy (Kasai procedure) and often, ultimately, liver transplantation. The major differential diagnosis includes neonatal hepatitis of various causes.

Patient preparation for cholescintigraphy should include phenobarbital to activate liver excretory enzymes and increase bile flow. With cholescintigraphy, biliary atresia images show a high-grade biliary obstruction, that is, a persistent hepatogram and no biliary-to-bowel transit over 24 h. The negative predictive value of the study is high, approaching 100%. The positive predictive value is said to be lower, and reports have given variable results, on average about 75% (*78*). False-positive results occur in some patients with severe parenchymal liver disease, that is, neonatal hepatitis of various causes.

A recently published 20-y experience with 186 infants at a pediatric referral center suggested that if patients receive phenobarbital, 5 mg/kg/d for the full 5 d, and have a serum phenobarbital level of more than 15 μg/mL before the ^{99m}Tc cholescintigraphy study, the specificity of the study is very high, with few false-positive results (*79*).

Cholescintigraphic images should be acquired at multiple times on the day that the ^{99m}Tc-HIDA agent is injected. Acquisition of only infrequent images can miss biliary-to-bowel transit. Imaging

up to 24 h is recommended. Evidence for intestinal activity at any time is diagnostic. Gallbladder filling has the same importance as intestinal activity. With the high back-pressure of the high-grade obstruction seen in biliary atresia, no bile secretion is seen. SPECT/CT can be quite helpful (*27,80*). A short SPECT acquisition of 10 min can be diagnostic in uncertain cases (Fig. 5).

[Fig. 5]

CONCLUSION

For almost 4 decades, cholescintigraphy has been a valuable frequently requested diagnostic radionuclide imaging study. Present-day indications and methodologies have been described, as well as important pharmacologic interventions.

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