Cholecystokinin Cholecystography in the Diagnosis of Gallbladder Disease

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Twenty-six patients who had typical symptoms of biliary tract disease, *e.g.* postprandial right upper quadrant pain, nausea and vomiting, fatty food intolerance and flatulence and who had had two or more normal oral cholecystograms were subjected to cholecytokinin cholecystography. Ten patients showed a normal response to the intravenous administration of cholecystokinin, namely prompt and complete emptying of the gallbladder without producing any adverse reaction or symptoms. Sixteen patients demonstrated either no contraction or incomplete contraction of the gallbladder in response to cholecystokinin; several patients had moderate contraction of the gallbladder accompanied by symptoms of biliary colic. This latter group underwent cholecystectomy and operative cholangiography. Fifteen of the 16 patients are asymptomatic or improved, and only one patient continues to have symptoms. All removed gallbladders had histologic evidence of chronic cholecystitis. It is concluded that in some individuals with continuing symptoms suggesting gallbladder disease but normal oral cholecystograms, cholecystokinin cholecystography may be helpful in identifying physiologic dysfunction of the gallbladder.

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ALL SURGEONS ARE FAMILIAR with the patient who describes postprandial upper abdominal colicky pain, nausea and flatulence and who also describes fatty food intolerance, but whose oral cholecystogram is "within normal limits." In many instances, ultrasonography of the upper abdomen has also demonstrated a normal gallbladder without evidence of stones. Additional diagnostic studies have failed to disclose any abnormalities, so the patient has been treated for symptoms with a variety of medications without great success.

Over the past four years, 26 patients with symptoms typical of gallbladder disease, but whose routine diagnostic studies have not supported the diagnosis have been identified. All of these patients have been subjected to cholecystokinin cholecystography in an attempt to identify physiologic dysfunction of the gallbladder to explain the patient's symptoms. These patients form the basis of this report.

Clinical Material

There were 26 patients in this group, 20 females and four males. The age range was 22–81 years. All of the patients complained of abdominal pain, but other symptoms such as fatty food intolerance or nausea and vomiting were less prominent (Table 1). They had all had at least two oral cholecystograms which were interpreted as normal. Various means of relieving the symptoms had been tried including fat-free diets, anticholinergic drugs, tranquilizers and other medications, all without success.

Because of continuing symptoms, all patients were subjected to cholecystokinin cholecystography. In this examination, the patient receives either six Telepaque® tablets the evening before the roentgenogram or six tablets each evening on two successive days prior to the x-ray (reinforced oral cholecystography). When the film clearly demonstrates a well visualized gallbladder, and there is no evidence of stones within the gallbladder, the patient is given 0.02 mg/kg of the C-terminal octapeptide of cholecystokinin (Kinevac®) intravenously. Gallbladder roentgenograms are obtained at five, ten and 15 minutes after injection.[15] The gallbladder is evaluated for contraction from these films, and the patient is monitored for the development

Presented at the Annual Meeting of the Southern Surgical Association, December 3–5, 1979, Hot Springs, Virginia.

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Submitted for publication: December 7, 1979.

0003-4932/80/0500/0636 $00.75

TABLE 1. *Symptoms*

	Operative Group (%)	Nonoperative Group (%)
Abdominal pain	100	100
Fatty food intolerance	48	40
Nausea and vomiting	48	30
Biliary colic	19	20
Dyspepsia	13	10

of symptoms suggesting an abnormality of the biliary tract. The symptoms looked for are a reproduction of those complaints the patient had voiced in the past. The lack of gallbladder contraction or spastic contractions without at least 50% emptying within 15 minutes was considered as a positive indication that there was an abnormality of the gallbladder, the cystic duct or both.[12]

Results

Ten patients showed no abnormalities in response to cholecystokinin administration, *i.e.* the gallbladder contracted promptly without producing any symptoms (Fig. 1A and B). Three patients in this group were found to have esophageal carcinoma, diffuse gastritis, and achalasia on further evaluation. One patient had become asymptomatic at the time of a gastric bypass eight months later, and her gallbladder appeared grossly normal at that procedure. In the remaining six patients, no explanation for the symptoms has been found. None of the patients have had cholecystectomy.

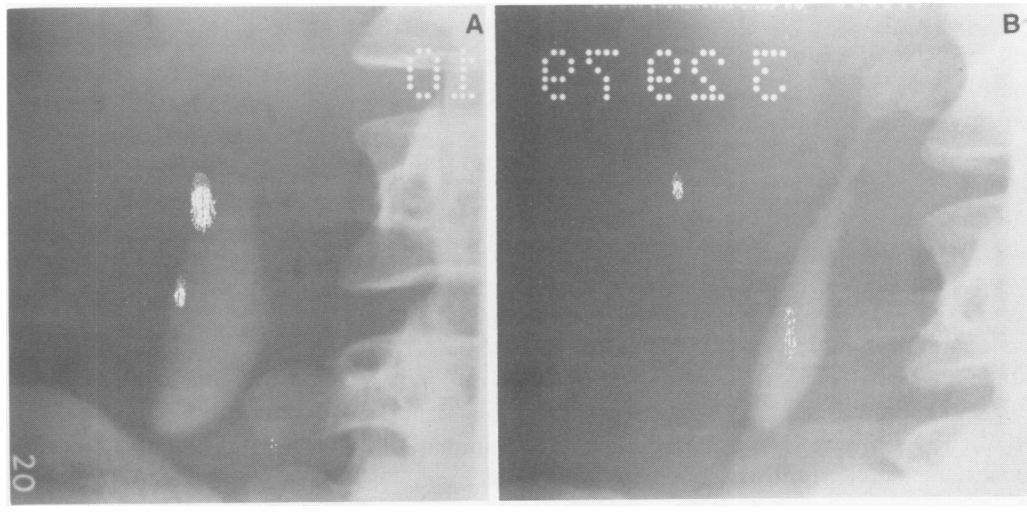
Sixteen patients demonstrated an abnormal response to intravenous cholecystokinin by either reproduction of the patient's symptoms, spastic contraction of the gallbladder without emptying or less than 50% reduction in size within 15 minutes of injection (Figs. 2A and B). All of these patients were subjected to cholecystectomy and operative cholangiography. None of the patients had gallstones, but several of the cystic ducts were described as narrowed. Cholangiograms showed no abnormalities of the biliary tree and good emptying into the duodenum. Histologic examination clearly demonstrated changes associated with chronic cholecystitis in all resected gallbladders.

Follow-up of these 16 patients has been 100% for 7–38 months with an average of 18 months. One patient continues to complain of postprandial nausea and vomiting, the symptoms she had before cholecystectomy; two patients experience occasional mild postprandial pain or some indigestion; and 13 are asymptomatic and able to eat anything without discomfort.

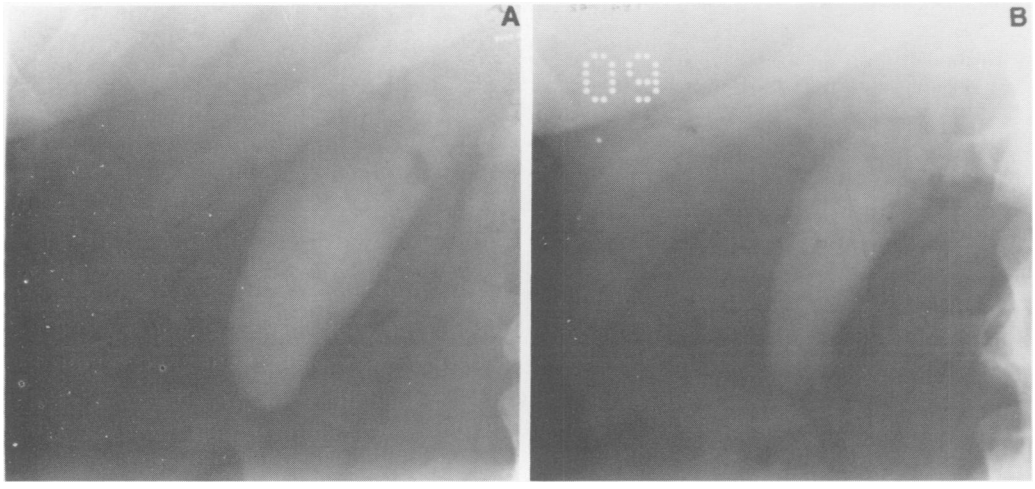
Discussion

Before the advent of oral cholecystography, the "classical" symptoms of postprandial upper abdominal colicky pain associated with fatty food intolerance, flatulence and nausea led to the clinical diagnosis of gallbladder disease. Often it was necessary to await more severe symptoms before cholecystectomy was undertaken. However, many patients had their gallbladder removed on the basis of these symptoms as well as others such as constipation or headache. It was also recognized that patients who were female, fat, and fertile often had biliary tract disease. Many of the gallbladders removed under these circumstances contained stones and most had an abnormal histologic picture. The majority of the patients were helped by cholecystectomy although some continued to have the same complaints, and a few developed even more symptoms which were difficult to treat; these persistent symptoms were given the name postcholecystectomy syndrome.

In 1924 Graham and Cole described roentgenographic opacification of the gallbladder by giving a



FIGS. 1A and B. (A) Gallbladder before cholecystokinin injection. (B) Gallbladder 15 minutes after cholecystokinin injection. Note more than 50% contraction.



FIGS. 2A and B. (A) Gallbladder before cholecystokinin injection. (B) Gallbladder 15 minutes after cholecystokinin injection. Note virtually no change in size.

substance orally which was absorbed and eventually concentrated in gallbladder bile.[8] Radiolucent stones were easily seen in the gallbladder thus opacified, and were clear-cut evidence of gallbladder disease. Inability to visualize the gallbladder in the absence of gastrointestinal absorptive defects or liver disease was also evidence of a diseased gallbladder. The widespread application of oral cholecystography coupled with the increasing recognition of the inadequacy of relying on symptoms alone as well as the difficulties of the postcholecystectomy syndrome, eventually resulted in the dictum that cholecystectomy should be undertaken only when there was roentgenographic evidence of gallbladder abnormality. This rigid criterion for cholecystectomy in patients complaining of postprandial distress brought on by the ingestion of fat has undoubtedly resulted in the missed diagnosis of biliary tract disease as pointed out in 1966 by Farrar.[4]

Oral cholecystography is probably 90–95% accurate. Small stones may be missed and thus as many as 5–10% of patients with a "normal" oral cholecystogram may have cholelithiasis underlying their symptomatology. Moreover, standard oral cholecystography even with a fatty meal does not always elicit motor dysfunction of the gallbladder which may be seen in the so-called cystic duct syndrome.[2,3] This particular entity emphasizes the narrowing of the cystic duct probably related to subacute infection and fibrotic changes which interferes with the normal emptying of the gallbladder in response to a meal. If, during the emptying process, the pressure within the gallbladder becomes markedly elevated, right upper quadrant colicky pain will be experienced by the individual. In this instance where there are minimal or no changes consistent with cholecystitis, the patient may be relieved of symptoms by cholecystectomy if this abnormality can be detected.

In 1928 Ivy and Oldberg described a humoral mechanism for the stimulation of gallbladder contraction which was caused by the presence of fat in the intestine.[10] The hormone was named cholecystokinin and eventually purified by Jorpes and Mutt in 1968.[11,13] However, porcine cholecystokinin had become available by 1958 for experimental use in patients. In that year Broden described the use of cholecystokinin in patients with a readily visualized gallbladder as a test of motor function.[1] Eleven years later the three postinjection responses described above were used as an indication of biliary tract disease.[12]

It is these responses or combinations of them which were used in the present series of 26 patients to identify those whose symptoms might be attributable to a physiologic dysfunction of the gallbladder.[9] Several recent articles and letters have reported on more than 100 patients who exhibited abnormal responses to cholecystokinin cholecystography and were subjected to cholecystectomy.[6,7] Relief of symptoms occurred in more than 90% of the patients which is similar to the experience reported here. Most of the patients who obtained symptomatic relief had gallbladders which showed chronic cholecystitis. However, some of the removed gallbladders were histologically normal or showed only mild cholecystitis, and in these patients the cause of symptoms may well have been a partial, but significant obstruction to bile flow out of the gallbladder in response to endogenous cholecystokinin. The resultant rise in gallbladder intraluminal pressure, perhaps sudden, would surely produce abdominal pain or colic and might lead to nausea or vomiting. Failure of cholecystectomy to relieve symptoms after a positive cholecystokinin cholecystogram may be due to the fact that the abnormality resides at the sphincter of Oddi with papillitis or fibrosis there causing obstruction to bile outflow in response to cholecystokinin.

Needless to say, selection of patients for cholecys-

tectomy under these circumstances must be highly individualized. First, a careful history must elicit the symptoms of true biliary colic with some relation to food ingestion. Other diseases of the gastrointestinal tract must be ruled out; the patient's overall psychological makeup and their home and job situation should be known.[7] At least one standard oral cholecystogram which clearly visualizes the gallbladder must be performed before undertaking cholecystokinin cholecystography. All of the patients in this series had at least two oral cholecystograms, and some had had several more than that with the highest number of oral cholecystograms performed on a single patient being five. When discussing the operation with a patient, it must be clear that the patient's symptoms may not be alleviated by the operation although as indicated from the results in this series the chances are good that relief will be obtained.

Cholecystokinin cholecystography is not the only test available for the diagnosis of occult or otherwise inapparent gallbladder disease. Bile discharged into the duodenum after the administration of cholecystokinin can be collected and examined for cholesterol crystals, leukocytes, and bacteria all of which may be indicative of gallbladder abnormality. Examination of duodenal bile is an old method of detecting gallbladder disease but the addition of cholecystokinin stimulation of gallbladder contraction has increased the sensitivity of the test.[5–7,14] It may be used in conjunction with the roentgenographic studies. In the patient with persistent symptoms further diagnostic techniques may be necessary to establish a diagnosis, *e.g.* endoscopy, retrograde pancreaticocholangiography or even angiography. Persistence of symptoms in three of the ten patients with symptoms suggesting biliary tract disease but normal oral and cholecystokinin cholecystography eventually led to tests which demonstrated significant lesions.

The intent of any of these diagnostic maneuvers should be not only to detect biliary tract abnormalities correctly but also to aid in the identification of patients whose psychosomatic illness is manifest as biliary colic. It is as important to diagnose motor dysfunction of the gallbladder which can be effectively treated by cholecystectomy as it is to identify those individuals who should not be operated on, and cholecystokinin cholecystography seems to be a simple test which can be used as an additional diagnostic maneuver for those difficult patients whom all surgeons see from time to time.

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Discussion

Dr. Monford D. Custer, Jr. (Winchester, Virginia): I think the reason that Dr. Griffen was kind enough to invite me to preview his manuscript was that some time ago we had the pleasure of sharing a few days at Sea Island, I told him that we have embarked upon a study of some 3000 consecutive cholecystectomies in an effort to identify those among them which were performed for noncalcus disease.

And I really can't tell you very much about this because we're not very far down the road as yet. But I can tell you that the incidence in this series surprised me a little bit, being one in ten. Thus we have 300 such cases, which we have turned over to our Pathology Department for data retrieval.

I can also tell you —and this reassures me a little bit—that the incidence of disease among these is rather reassuringly high, the disease being almost invariably either cholesterolosis, or mild chronic cholecystitis.

Now, I would loosely guess that perhaps once a year a surgeon who is interested in biliary tract disease will encounter such a patient as Dr. Griffen has described. It's a woman, usually, and she has classic, typical biliary tract symptoms, and they may be of major proportion, in the face of a series of normal cholecystograms and correspondingly negative ultrasonograms.

What one does in this situation is to make an attempt to get to know the patient, and over a period of, perhaps, six months or 12 to make up your own mind as to whether, in point of actual fact, she does have significant symptomatology. And then, having reached that conclusion, you sit down with her, and you tell her that, at least occasionally, there are other noncalculous disorders of the gallbladder which can produce this type of symptomatic trouble.

And you say to her: If you want to take a chance, I'll take a