Incidence and Morbidity of Cholelithiasis in Patients Receiving Chronic Octreotide for Metastatic Carcinoid and Malignant Islet Cell Tumors

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BACKGROUND. Octreotide, a long-acting somatostatin analogue, has demonstrated clinical utility in patients with carcinoid syndrome and malignant islet cell tumors of the pancreas. Prior studies have reported a greater than expected incidence of cholelithiasis in patients treated with octreotide for acromegaly. This study attempted to determine the incidence and morbidity of cholelithiasis in a group of patients with metastatic carcinoid or malignant pancreatic islet cell tumors who were receiving chronic therapy with octreotide.

METHODS. Forty-four of 55 patients on investigational protocols with octreotide were eligible for chart review; 10 patients were excluded due to prior cholecystectomy and 1 patient due to asymptomatic cholelithiasis at presentation. Patients fell into three treatment groups. The low dose (LD) group was comprised of 17 patients receiving 150 μg of subcutaneous octreotide 3 times a day. Twenty-one patients received high dose (HD) therapy comprised of 500 μg given 3 times a day. The low dose-high dose (LD-HD) group was comprised of 6 patients who had their dose escalated from 150 μg to 225–500 μg of octreotide 3 times a day.

RESULTS. The overall incidence of cholelithiasis and/or gallbladder sludge was found to be 52.3% in all 3 treatment groups. Three of the 44 patients (6.8%) had symptomatic disease requiring emergency cholecystectomy. Five other patients underwent elective or incidental gallbladder surgery. The incidence of cholelithiasis in the LD, LD-HD, and HD groups was 35.3%, 66.6%, and 61.9%, respectively. The incidence of acute cholecystitis in the three groups was 11.8%, 0%, and 4.8%, respectively.

CONCLUSIONS. Although greater than 50% of patients receiving octreotide developed cholelithiasis, a much smaller percentage of patients had symptomatic gallbladder disease. Patients receiving chronic octreotide treatment require monitoring for the development of gallstones. However, prophylactic cholecystectomy is not indicated, unless it is performed in conjunction with bowel resection or cytoreductive hepatic surgery. ***Cancer* 1997; 79:830–4.**

KEYWORDS: cholelithiasis, octreotide, metastatic carcinoid, islet cell tumors, cholecystitis.

The long-acting somatostatin analogue octreotide has been used successfully in the management of a variety of benign and malignant tumors. Octreotide has been useful as adjuvant therapy to surgery and radiation, and as primary therapy in nonoperable patients with acromegaly.[1,2] Symptomatic relief and tumor regression have been demonstrated in patients with metastatic carcinoid and various hormone-producing malignant islet cell tumors of the pancreas.[3–5] This drug has also demonstrated utility in controlling diarrhea in

scleroderma[6] and acquired immune deficiency syndrome,[7] as well as in the preoperative prevention and management of carcinoid crisis.[8,9]

In 1977, two separate investigators reported a somatostatin-producing pancreatic islet cell tumor,[10,11] and the somatostatinoma syndrome was subsequently described.[12] In all the original case reports, cholelithiasis was a major clinical manifestation. Therefore, the same side effect from supraphysiologic doses of a long-acting analogue of this naturally occurring 14-amino acid peptide could be predicted. In most of the case reports, cohort reports, and clinical trials of octreotide reported to date, cholelithiasis has been a major side effect of therapy.[1,2,13–17]

To the authors' knowledge, prior to this report, all studies of the incidence and morbidity of cholelithiasis have been conducted on patients with acromegaly. The incidence of cholelithiasis has ranged from no greater than in the general population[18] to 50–60%.[2,19] This investigation attempts to report the incidence, duration of therapy before evidence of gallstones, symptoms from gallstones, and need for cholecystectomy in a group of patients receiving long term octreotide therapy for metastatic carcinoid or malignant islet cell tumors of the pancreas.

METHODS

Fifty-five patients, returning for routine follow-up during a 6-month period in 1990, were identified under octreotide treatment protocols for metastatic carcinoid and malignant islet cell tumors. Ten of the 55 patients had cholecystectomy prior to the start of octreotide therapy, and were not considered in the analysis. All of the patients had undergone a computed tomography (CT) scan or an ultrasound scan of the abdomen prior to treatment. One patient was found to have asymptomatic cholelithiasis prior to beginning therapy, and therefore was also excluded. Data were collected on 44 patients. This group was divided into 3 groups based on the dose of octreotide received; 17 patients were in the low dose (LD) treatment group, 6 patients who were initially in the low dose group had their doses increased (LD-HD), and 21 patients received high dose (HD) therapy. Signed informed consent was required for all patients entered on a study protocol using octreotide.

LD therapy patients self-administered 150 μg of octreotide subcutaneously, 3 times a day. Enrollment in the LD study began in 1984. Within this LD treatment group, the dose of octreotide was able to be escalated in six patients depending on the clinical and biochemical response. For these patients, the dose increased from 150 μg 3 times a day to 225–500 μg 3 times a day (LD-HD group). Enrollment in the HD treatment group began in 1986. Patients in this group received 500 μg of octreotide subcutaneously 3 times a day. Only two patients received escalation of this dose, and were followed in the HD group.

The octreotide treatment studies were open to patients with metastatic carcinoid tumors or islet cell carcinoma and no prior history of somatostatin therapy. The octreotide studies required the patients to have objective measurements of tumor response either by linear tumor measurement, laboratory measurement of urinary 5-hydroxyindoleacetic acid, or pathologic circulating hormone levels. Therapy could be discontinued at 4 weeks or anytime thereafter if disease progression was evident. If a favorable objective or symptomatic response was obtained, treatment could be continued indefinitely until disease progression was evident. If a patient demonstrated symptomatic improvement in the face of objective tumor progression, the treatment then could be continued at the discretion of the treating physician and the principal investigator. Patients continued to undergo treatment for at least 12 weeks if the tumor and symptomatic status were both stable. After that time, treatment could continued or stopped at the discretion of the physician, depending on the clinical impression of the treatment value to the patient.

The charts of these 44 patients were reviewed. Information concerning dose of octreotide, length of therapy, results of initial abdominal imaging study (CT scan, magnetic resonance imaging [MRI] scan, or ultrasound scan), subsequent gallbladder studies, symptoms from gallbladder disease, and whether elective or emergency cholecystectomy was performed, was retrospectively extracted from the clinic records. Surgical and pathology reports were reviewed in all patients who underwent cholecystectomy. Only 11 of 44 patients (25%) underwent an ultrasound examination of the gallbladder prior to starting therapy. Ultrasound and CT scans were performed periodically, but not uniformly in all patients receiving treatment. During 1 6-month period in 1990, 31 of the 44 patients returning for routine follow-up underwent a gallbladder ultrasound. A CT or ultrasound scan that documented gallstones was considered positive. The occurrence of debris or ''gallbladder sludge'' also was documented.

RESULTS

Table 1 shows the results for the three patient groups. The overall incidence of cholelithiasis and/or the presence of gallbladder sludge in the patients treated with octreotide was 52.3% (23 of 44 patients). Four patients (9.1%) only had gallbladder sludge on ultrasound. The median time from the start of treatment to the occurrence of cholelithiasis was 28 months for all treatment

TABLE 1
Results for the Three Patient Groups

	Group		
	LD	LD-HD	HD
No.	17	6	21
Age (yrs) (means)	54.1	53.5	55.1
Male/female	10/7	5/1	13/8
Time of US (mos)[a]			
Median	33.0	36.0	36.0
% GS present (no.)	35.3 (6)	66.6 (4)	61.9 (13)
% GB sludge only	0	33.3 (2)	9.5 (2)
Time to GS (mos)[b]			
Median	42.0	50.0	27.8
Range	19–62	9–60	2–46
% Symptomatic (No.)[c]	17.6 (3)	0.0	9.5 (2)
Acute cholecystitis	11.8 (2)	0.0	4.8 (1)
% GB removed (No.)	17.6 (3)	33.3 (2)	14.3 (3)
Mos followed			
Median	42.0	45.5	46.0
Range	18–84	44–77	21–66

LD: patients receiving low dose octreotide (150 μg, 3 times a day); LD-HD: patients initially receiving low dose octreotide with subsequent dose escalation; HD: patients receiving high dose octreotide (500 μg, 3 times a day); US: ultrasound; GS: gallstones and/or gallbladder sludge; GB: gallbladder.

[a] Time of ultrasound refers to the time from onset of therapy to when the first follow-up gallbladder imaging was performed.

[b] Time to gallstones and/or gallbladder sludge refers to the time from onset of therapy to when cholelithiasis and/or gallbladder sludge was documented.

[c] % Symptomatic refers to both acute and chronic biliary symptoms.

groups. Only 3 of the 44 patients (6.8%) had acute symptomatic cholelithiasis. These patients required emergency cholecystectomy. Five other patients had elective cholecystectomy, two for intermittent biliary colic.

In the LD treatment group, 6 of 17 patients (35.3%) were found to have gallstones. Two patients within this group (11.8%) had acute symptomatic biliary disease. One patient had acute cholecystitis, requiring emergency surgery, 9 months after ultrasound documentation of gallstones. Another patient presented with an acute abdomen; no gallstones were seen on the preoperative ultrasound or at the time of surgery, but pathologic examination of the gallbladder revealed acute cholecystitis. One patient had elective cholecystectomy for intermittent biliary colic. At the time of surgery, this patient had 50 mixed gallstones, and the gallbladder wall showed mild chronic inflammation.

For the LD-HD patients, 4 of the 6 patients (66.6%) were found to have gallstones and/or gallbladder sludge (2 patients had gallbladder sludge only). The median time the patients were on LD therapy before accelerating to HD therapy was 17 months (range, 8–30 months). No patient in this group had symptomatic disease. Two patients underwent elective cholecystectomy, one at the time of bowel resection and the other at the time of hepatic lobe resection.

In the HD treatment group, 13 of 21 patients (61.9%) had cholelithiasis and/or gallbladder sludge. Two patients had gallbladder sludge only on ultrasound examination. Only 1 patient in this group required emergency cholecystectomy after 24 hours of acute right upper quadrant pain. At laparotomy, the patient was found to have a perforated and gangrenous gallbladder with multiple mixed gallstones. An additional two patients underwent elective gallbladder removal. One patient had intermittent biliary colic; numerous mixed gallstones were recovered. The other patient had multiple, calcium-containing stones at the time of hepatic resection and peritoneal debulking for a widely metastatic carcinoid tumor. The one patient who had cholelithiasis documented before beginning octreotide therapy did not develop any symptoms while on treatment.

The median time from starting octreotide therapy to when a gallbladder imaging study was performed was similar for all groups: LD: 33 months; LD-HD: 36 months; and HD: 36 months. An inverse relationship between the dose of octreotide and the median time to documentation of cholelithiasis was noted between the LD and HD groups (LD: 42 months [range, 19–62 months]; LD-HD: 50 months [range, 9–60 months]; HD: 27.8 months [range, 2–46 months]). This suggests that the higher the dose of somatostatin, the faster the rate of gallstone formation. However, because the follow-up CT and ultrasound scans were not performed uniformly, and most of the patients were asymptomatic, this conclusion cannot be firmly made.

DISCUSSION

The major pathogenic mechanism of gallstone formation by octreotide is the postprandial inhibition of cholecystokinin (CCK) release from the small bowel mucosa. Inhibition of CCK causes gallbladder hypomotility and stasis.[20,21] Animal and human studies suggest that octreotide can also cause alterations in bile composition, leading to cholelithiasis.[22]

In a review article by Dowling et al. regarding cholelithiasis and octreotide therapy, the authors present data in support of the assumption that gallstones secondary to octreotide therapy are cholesterol rich.[23] Indirect evidence comes from the observation that most gallstones are radiolucent on plain X-rays; Hounsfield units, measured by CT scan of gallbladder material, tend to be lower in this group of patients, and there are case reports of gallstone dissolution by oral bile acid, ursodeoxycholic acid.[23,24] In the current study, eight patients underwent gallbladder resection; seven of these patients' records made mention of gallstone

composition. Five patients had mixed gallstones, but the cholesterol percentage was not measured. One patient had milk of calcium sludge with numerous, minute, calcium-containing stones; another patient had acute cholecystitis without any gallstone or sludge material within the gallbladder. More information concerning the composition of gallstones in patients receiving somatostatin analogue treatment need to be obtained to better direct treatment and prevention therapies.

Several factors may play a role in the prevention of cholelithiasis in patients receiving octreotide. Because octreotide only suppresses postprandial CCK release, while leaving fasting CCK levels near normal,[25] avoiding octreotide administration around meal time may improve gallbladder emptying. However, it has been demonstrated that between 4 and 8 hours are required before normal meal-stimulated response to CCK returns.[26] Another study demonstrated that a weekly drug free interval may improve gallbladder emptying, with rebound biliary hypermotility.[27] This approach would not be practical in patients such as those in the current study with hormonally active tumors because symptoms of the endocrinopathy would recur. The therapeutic and prophylactic use of ursodeoxycholic acid needs further study, as well as agents such as nonsteroidal antiinflammatory drugs that have the potential to prolong nucleation time and prevent gallstone formation.[28]

The current study may potentially overestimate the incidence of cholelithiasis. Ultrasonography is currently accepted as the most sensitive noninvasive method for detecting gallstones.[29,30] Only 25% of the patients had a pretreatment gallbladder ultrasound, and most of these patients were in the HD group. The rest of the patients had CT or MRI scans of the abdomen. Routine CT scanning of the abdomen has a sensitivity of $< 50\%$ for detecting gallstones.[30] Therefore, more patients than realized may have had cholelithiasis before beginning therapy with octreotide. However, the incidence of symptomatic disease and acute cholecystitis should be unaffected. Current study protocols with a somatostatin analogue now incorporate a pretreatment ultrasound examination of the gallbladder.

The incidence of cholelithiasis and/or gallbladder sludge found in the patients with metastatic carcinoid or malignant islet cell tumors undergoing octreotide therapy in this study was 52.3%. Four patients (9.1%) had only gallbladder sludge documented. As mentioned earlier, prior studies on the incidence of gallstones in acromegalics varied from approximately 15%, which is the expected proportion that should be found in a normal population,[14,18,31] to 50–60%.[2,15,19,32] In the previously mentioned review by Dowling et al., the author reviewed ten reports of cholelithiasis in acromegalics receiving octreotide therapy, and calculated the rate of new gallstone formation, without factoring the dose or length of treatment, to be 29%.[23] The incidence in the current study is in agreement with the incidence observed for acromegalics receiving octreotide.

The current study also suggests a dose-effect relationship between the dose of octreotide and the incidence of gallstones. The LD group had a 35.3% incidence of gallstones and/or gallbladder sludge compared with the HD group, in whom the incidence was 61.9%. This has not been demonstrated in any of the previous studies. The use of the lowest possible dose of octreotide to achieve the desired therapeutic benefit might decrease the likelihood of cholelithiasis.

Although the overall incidence of cholelithiasis in patients receiving long term octreotide may approach 50%, the incidence of symptomatic biliary disease is much less. None of the previously mentioned studies demonstrated a $>20\%$ incidence of gallstones producing symptoms. In the current study, only 11.4% of patients required cholecystectomy for biliary symptoms. Patients receiving octreotide need to be aware of the potential biliary side effects of treatment. Until more clinical experience is available, monitoring for the development of cholelithiasis by ultrasonography should be a routine part of medical follow-up care in these patients. The results of this study and previous studies do not support the need for prophylactic cholecystectomies in patients who develop asymptomatic cholelithiasis. However, in patients with metastatic carcinoid or malignant islet cell tumors, cholecystectomy should be performed if the patient is undergoing surgery for bowel resection or cytoreductive hepatic surgery.[33]

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