Recurrent Pancreatitis After Treatment With Hydrochlorothiazide

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The cause of acute pancreatitis is usually readily apparent after a basic examination. The most common causes of pancreatitis are cholelithiasis and alcoholism, which account for 75 to 80 percent of all cases.¹ In approximately 10 percent of cases, no cause is found.^{2,3} Other causes of pancreatitis include trauma, the postpartum and postoperative states, toxins, hyperlipidemias (types I, IV, V), hypercalcemia, hyperparathyroidism, peptic ulcer disease, endoscopic retrograde cholangiopancreatography (ERCP), and certain infections (mumps and coxsackievirus).^{1,3,4} Many drugs have been shown or presumed to cause pancreatitis (Table 1). Chlorothiazide was introduced in 1958 and is an effective, widely prescribed, and generally well tolerated antihypertensive agent. Soon after the introduction of chlorothiazide, an association with pancreatitis was observed.5 The patient presented here had two discrete episodes of pancreatitis attributable to thiazide diuretics.

Case Report

The patient was a 43-year-old man who had a history of hypertension, gout, and pancreatitis of unknown cause in 1985. At that time he was taking hydrochlorothiazide, triamterene, and pindolol for hypertension. Findings on a gall bladder sonogram were normal, and no cause for the pancreatitis was determined. The patient was prescribed only pindolol at discharge. In 1989 the patient's antihypertensive medication was changed to 400 mg of labetalol and 50 mg of hydrochlorothiazide. In July 1991 the patient changed physicians, and the thiazide diuretic was discontinued. In early 1992 the patient's blood pressure was not adequately controlled by labetalol alone, and 50 mg of hydrochlorothiazide was again prescribed. Within 1 month he came to

the emergency department with acute epigastric pain and recurrent vomiting.

The patient had a history of mild hypertriglyceridemia, consumed three alcoholic drinks a month, and had no history of biliary tract disease. On examination the patient was a large muscular man in extreme distress. His blood pressure was 172/113 mmHg, respirations were 24/min, temperature was 98.8°F (37.1°C), and weight was 242 lb (110 kg). His abdomen had no bowel sounds and was slightly distended. He had extreme tenderness in the epigastric area with marked guarding. No masses were palpable. Laboratory studies revealed the following values: an amylase of 1131 U/L, lipase 11,063 U/L, glucose 204 mg/dL, lactate dehydrogenase 483 U/L, and a white cell count of 18,900/µL3. His calcium level was 10.1 mg/dL, phosphorus was 3.3 mg/dL, and triglycerides were 276 mg/dL.

He was admitted to a community hospital, where a nasogastric tube was inserted, intravenous fluids were initiated, and parenteral meperidine was administered. An ultrasonic examination of his gallbladder was normal. On the 2nd hospital day a computerized tomogram (CT) showed severe necrotizing pancreatitis. His temperature was 101.1°F (38.4°C); at this time the laboratory values were white cell count 20,400/ μ L, amylase 298 U/L, lactate dehydrogenase 1776 U/L, glucose 137 mg/dL, and calcium 7.8 mg/dL. Blood and urine specimens were cultured, empiric cefoxitin therapy was initiated, and a clonidine patch was applied.

On the 7th hospital day total parenteral nutrition was begun; the patient did not require insulin. All cultures were negative. A second CT scan showed phelgmous changes in the peripancreatic fat, with necrosis of the body of the pancreas and development of a 5-cm fluid collection in the lesser sac. Clinically, the patient improved, and his amylase level returned to normal. On the 10th hospital day he had a severe episode of abdominal pain. A third CT scan showed further pancreatic destruction and several cystic areas in the head

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| Table 1. | Drugs | Associated | with | Pancreatitis. |
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| Definite Association | Possible Association | | |
|----------------------|--|--|--|
| Sulfonamides | L-Asparaginase | | |
| Thiazide diuretics | Chlorthalidone | | |
| Furosemide | Corticosteroids | | |
| Estrogens | Ethacrynic acid | | |
| Tetracycline | Phenformin | | |
| Pentamidine | Procainamide | | |
| Valproic acid | Nonsteroidal anti-inflammatory agents | | |
| Didanosine (DDI) | Nitrofurantoin | | |
| Mercaptopurine | Metronidazole | | |
| Azathioprine | | | |

and body of the pancreas with no air fluid levels. Additional analgesics were administered and the pain subsided.

On the 18th hospital day the patient developed increasing abdominal pain and his serum amylase increased to 640 U/L. He was transferred to a tertiary care center. A CT scan showed a 20-cm fluid collection around the pancreas. His white cell count had increased to $31,000/\mu$ L. The patient underwent surgical drainage of the pseudocyst and débridement of the necrotic pancreas and peripancreatic necrotic tissues. Forty-eight hours later a second débridement was performed, and the patient was found to have a necrotic posterior gastric wall. He underwent a midgastrectomy and cholecystostomy. A third débridement was performed, and a jejunostomy tube and a gastrostomy tube were inserted.

The patient improved and was discharged after a total hospitalization of 6 weeks. He was discharged with a gastrostomy tube, a jejunostomy tube, a cholecystostomy, and three Jackson Pratt drains. Five months after admission he underwent an antrectomy, reconstruction of gastrointestinal continuity with Roux-en-Y gastrojejunostomy, cholecystectomy, and closure of tube jejunostomy. Two 4-cm pseudocysts were discovered and drained. Six months after admission the patient had lost 25 percent of his body weight and had developed a pancreaticocutaneous fistula.

Discussion

A challenge test is the most reliable evidence that a specific medication causes pancreatitis. The test involves documenting that pancreatitis develops during treatment with the drug, disappears after discontinuation of the drug, and recurs when the drug is re-introduced.⁶ During treatment of his hypertension this patient was unintentionally rechallenged with a thiazide diuretic and had a second episode of pancreatitis. Positive challenge tests have been reported for the loop diuretic furosemide.⁷ No positive challenge tests with thiazide diuretics could be found on the MEDLINE data base. The intentional rechallenge of a patient should occur in a controlled research setting and has no diagnostic or therapeutic role in clinical practice.

There is experimental and clinical evidence that thiazide diuretics cause pancreatitis. In 1961 Cornish, et al.8 studied amylase levels in 20 patients who were taking 1 to 2 g of chlorothiazide a day and found elevated levels in 50 percent of the study subjects. The amylase levels increased more than 100 percent in the thiazide-treated patients. No patients exhibited signs or symptoms of pancreatitis. Amylase levels returned to normal when the drug was discontinued. Chlorothiazide was administered to 300 mice 6 days a week at a dosage of 0.02 g/d (equivalent to 1 g/d for a 70-kg human). Twenty-one of the mice had inflammatory pancreatic lesions, 15 animals had mild pancreatitis, and 7 had severe pancreatitis. The most severe lesions were found in those mice taking the drug the longest.⁸ More recently the medications of 100 patients admitted for acute pancreatitis were compared with medications of 100 matched patients admitted for abdominal pain who had normal amylase levels. Diuretic therapy was more common in the pancreatitis group, and the difference achieved statistical significance. The difference was due almost entirely to greater numbers of patients with pancreatitis taking cyclopenthiazide.9

The first cases of pancreatitis associated with thiazide use were reported in 1959.⁵ More recently a total of 13 cases of pancreatitis in nonpregnant patients have been reported or reviewed. The average age in one series was 68 years, and all patients had hypertension and arteriosclerotic heart disease, and two-thirds had congestive heart failure.¹⁰ In the second series, the patients had hypertension but were free of other important illnesses.¹¹ Patients developed pancreatitis anywhere from 21 days to 5 years after beginning therapy with a thiazide. The mean dose was 250 to 1000 mg of chlorothiazide or the equivalent of hydrochlorothiazide. Five of the 13

patients died from complications of pancreatitis. Two patients developed chronic pancreatitis during therapy with a thiazide diuretic. In one case the patient was also taking prednisone; which of the two drugs was responsible for the pancreatitis was not clear.¹² The other case was a 9-year-old boy who died of rheumatic heart disease while taking hydrochlorothiazide and was found at autopsy to have pathologic changes of chronic pancreatitis.¹³ As the present case illustrates, the clinical course of a patient with thiazide-induced pancreatitis can be severe. Thiazides generally cause hemorrhagic or necrotic pancreatitis. The clinical appearance of a patient who develops pancreatitis from thiazides is indistinguishable from that of patients with pancreatitis from other causes. Other than discontinuing the diuretic, the treatment of thiazide-induced pancreatitis is no different from other cases of pancreatitis.

The exact mechanism of thiazide-induced pancreatitis is unknown. Several possibilities have been suggested. Thiazides are well known to increase serum triglyceride levels.¹⁴ In some patients thiazides have been documented to increase serum calcium and decrease serum phosphorus levels.¹⁴ These alterations in calcium and phosphorus levels are also observed in hyperparathyroidism, and primary hyperparathyroidism is known to increase the risk of pancreatitis. It has been found at autopsy that some patients who developed pancreatitis during thiazide diuretic therapy have parathyroid hyperplasia.¹¹ Thiazides might act directly on the parathyroids or might affect both the parathyroid glands and the pancreas.¹¹

After this patient's initial episode of pancreatitis, no cause was determined. It has been reported that up to 20 percent of pancreatitis cases are idiopathic.⁴ Other sources have reported that 5 to 10 percent of cases are idiopathic.^{2,3} Carey¹ found that after a thorough examination few cases of pancreatitis are, in fact, idiopathic. Before diagnosing idiopathic pancreatitis in any patient, a meticulous search for other possible causes must be conducted.

This case illustrates the clinical course of a patient who had recurrent pancreatitis after treatment with a thiazide diuretic. Family physicians must be aware of the potential for thiazide diuretics and other drugs to cause pancreatitis. It is extremely important to obtain a complete medication history in patients seeking care for acute pancreatitis. Physicians must be cognizant of the role medications can play in the cause of acute pancreatitis and prescribe medications judiciously for patients who have a history of so-called idiopathic pancreatitis.

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