Case Report
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Acute pancreatitis, idiopathic versus drug-induced: a case report

Abstract

Acute pancreatitis is a sudden inflammatory process of the pancreas that may also involve peripancreatic tissues or remote organ systems.[1] It is associated with over 210,000 hospital admissions per year in the United States and the annual incidence of acute pancreatitis ranges from 5 to 80 cases per 100,000 persons, making it one of the most common gastroenterological conditions.[2,3] The highest incidence rates of acute pancreatitis are found in the United States and Finland.[3] Common causes include gallstones and heavy alcohol use, accounting for 30% to 60% and 15% to 30% of cases, respectively.[4] Other causes include smoking, hypertriglyceridemia, hypercalcemia, hyperparathyroidism, endoscopic retrograde cholangiopancreatography (ERCP), genetic mutations, trauma, surgery, infections and toxins, pregnancy, vascular disease, and drugs.[4–6] Although its occurrence is relatively rare, drug-induced pancreatitis has an estimated incidence of 0.1% to 2%. The true incidence of drug-induced pancreatitis is not known, as the evidence is mainly derived from case reports.[7] Additionally, reports have concluded that 5% to 20% of pancreatic cases are idiopathic.[6]

We describe a 48-year-old female with an extensive medical history who presents to the clinic with a three-day history of abdominal pain. She had no history of gallstones or alcohol use. She had been taking a combination of triamterene and hydrochlorothiazide for the past seven years and reported that her physician had recently increased her dosage because of uncontrolled blood pressure. Laboratory findings showed markedly elevated lipase and amylase and leukocytosis and radiographic imaging showed hepatomegaly with steatosis, but no evidence of cholelithiasis. Other causes of pancreatitis were considered. The patient received aggressive treatment with intravenous (IV) fluids, IV hydromorphone, placed on nothing by mouth (NPO) status, and hydrochlorothiazide was discontinued. Over the next 24hours, the patient's pain, leukocytosis, amylase, and lipase laboratory values all improved. This case report examines the possibility of drug-induced pancreatitis due to hydrochlorothiazide following an increase in the dose of the drug and determines that a meticulous search for other causes must be undertaken before a case is determined to be idiopathic.

Keywords: drug-induced, acute pancreatitis, hydrochlorothiazide, thiazides, idiopathic

Volume 4 Issue 2 - 2016

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Received: February 12, 2016 | **Published:** April 05, 2016

Introduction

Thiazides were among the first drugs discovered to be associated with pancreatitis.[8] Although there are several thiazide diuretics currently available, chlorthalidone and hydrochlorothiazide have been the two most commonly used diuretics in major clinical trials.[9] Hydrochlorothiazide was approved by the Food and Drug Administration (FDA) in 1959[10] and it continues to be the most popular in the management of high blood pressure.[11] Chlorthalidone was commonly used in the 1970s, but its use has sharply declined in the past 20years.[12] It is not known why chlorthalidone has fallen out of favor, however; studies support both hydrochlorothiazide and chlorthalidone as being very effective in the management of high blood pressure.[11]

There are experimental and clinical evidence that thiazide diuretics cause pancreatitis.[4,6–8,13–15] In fact, the first cases of pancreatitis associated with thiazides use were reported in 1959.[16] Since that time, other cases have been reported with patients who developed pancreatitis anywhere from 21days to five years after beginning therapy with a thiazide. The mean dose was 250mg to 1000mg of chlorothiazide or the equivalent of hydrochlorothiazide.[6] The unknowns are

i. Is the onset of drug-induced acute pancreatitis more likely to be associated with the initiation of the medication or

ii. Is the risk of a patient developing acute pancreatitis heightened after taking hydrochlorothiazide for several years, followed by an increase in dose?

Case presentation

A 48-year old female presents to the clinic with a three day history of abdominal pain. Twodays prior she experienced abdominal aches that were painful, constant, spastic, disabling her ability to walk completely upright due to pain. She described some pain relief when lying down in a bent over position. She thought the pain was due to gas and took simethicone orally, but the pain did not disappear. Instead, it progressively worsened the next two days, radiating straight through her abdomen and to the back. Once the pain became intolerable, she decided to go to the hospital.

Prior to admission, her pain score was a 5 on a scale of 1 to10 and her abdomen was distended and "hard and bloated." She denied any sick contact, fever, chills, or history of gallstones. The patient's past medical history was significant for depression (22years), cervical cancer (15years), broken jaw - mandible and maxilla (11years),

degenerative joint disease (9years), hypertension (9years), stabbed hand (3years), three pinched nerves (3years) and a torn rotator cuff (3years). The patient admits to taking a combination of triamterene 50mg and hydrochlorothiazide 25mg by mouth each day for the past seven years for management of hypertension. The dosage of this medication was recently increased by her primary care physician to triamterene 75mg and hydrochlorothiazide 50mg due to uncontrolled blood pressure. The patient could not remember the exact date of the increase, but stated that it was within the past 3months. In addition, she has a history of chronic pain due to three pinched nerves and is currently taking gabapentin 300mg three times daily, cyclobenzaprine 10mg four times daily as needed for muscle spasms, and hydrocodone 5mg and acetaminophen 325mg as needed for pain. The patient confirmed that she takes her benazepril, gabapentin, and triamterene and hydrochlorothiazide like "clock-work." She also mentioned the use of sertraline for depression, but said that she stopped taking it a while ago. She also takes lorazepam 1mg by mouth every night at bedtime as needed to treat anxiety. She denied the use of any herbal, nonprescription medications, alcohol, or illicit drugs. The patient has been a smoker for 30years and smokes 15-20 cigarettes per day.

On physical examination, the patient was obese (94.7kg, BMI 34), alert, and oriented. Gastrointestinal (GI) and skin exams revealed left-sided pain in the abdominal area, bowel sounds were present, there was tenderness in the right upper quadrant, a soft, distended abdomen, and a negative Murphy sign. An abdominal ultrasound imaging was performed to evaluate presence of cholelithiasis and the result was negative. Vital signs upon admission were as follows: temperature 97.60F, heart rate 85, and respiratory rate 18, blood pressure 112/71 mmHg. Laboratory tests were performed upon admission and on the next day (Table 1).

Table 1 Laboratory Findings

Laboratory findings	Upon admission	Next day	Reference value
White blood cell count (bil/L)	17.16	10.43	4 to11
Calcium (mMol/L)	2.5	2.2	2.12 to 2.62
Potassium (mMol/L)	3	3.3	3.5 to 5.0
Serum creatinine (mg/dL)	0.9	0.8	<1.3
Aspartate aminotransferase (U/L)	19	46	10 to 30
Alanine aminotransferase (U/L)	19	44	7 to 30
Amylase (U/L)	3,184	1,120	27 to 131
Lipase (U/L)	6,732	1,190	10 to 45
Cholesterol (mg/dL)		178	<199
Triglycerides (mg/dL)		152	<149
HDL (mg/dL)		31	>40
LDL (mg/dL)		118	<99

*Laboratory values from Institution Medical Center ***abnormal values***.

Based on the patient's clinical presentation (right upper quadrant and epigastric pain); laboratory findings (markedly elevated lipase and amylase >3 times the upper limit of normal and leukocytosis); radiographic imaging (hepatomegaly with steatosis, mildly prominent common bile duct, but no evidence of cholelithiasis); physical exam (bowel sounds present, soft, non distended, positive tenderness right upper quadrant pain, negative Murphy sign); (Table 2) and no history of gallstones or alcohol use, the patient was diagnosed with acute pancreatitis. All other causes of the disorder were ruled out and drug-induced versus viral versus idiopathic causes of pancreatitis were all considered (Table 2).

Table 2 Clinical Presentation and Evaluation

Clinical presentation	Evaluation
Signs & Symptoms	1. Right upper quadrant 2. Epigastric pain
Laboratory	1. Markedly elevated lipase and amylase >3 times the upper limit of normal 2. Leukocytosis
Radiographic imaging	1. Hepatomegaly with steatosis, mildly prominent common bile duct, but no evidence of cholelithiasis
Physical exam	1. Bowel sounds present, soft, non-distended, positive tenderness right upper quadrant pain, negative Murphy sign

Citation: Oelschlaeger LM. Acute pancreatitis, idiopathic versus drug-induced: a case report. *MOJ Public Health.* 2016;4(2):47–50.
DOI: 10.15406/mojph.2016.04.00075

The patient received aggressive treatment with intravenous (IV) fluids, IV hydromorphone 0.5mg every two hours for pain, was placed on nothing by mouth (NPO) status, and hydrochlorothiazide was discontinued. Over the next 24hours, the patient's pain, leukocytosis, amylase and lipase laboratory values all improved. She was discharged and advised to stay on a clear liquid diet for at least two more days before advancing to a soft diet, to avoid exacerbation of her abdominal pain, and to follow-up with her primary care physician in 5 to 7days.

Discussion

Viral causes for acute pancreatitis were ruled out since the patient did not have any other signs or symptoms associated with an infection, other leukocytosis. Abdominal ultrasound imaging revealed hepatomegaly with steatosis, mildly prominent common bile duct, but showed no evidence of cholelithiasis. Hepatomegaly is often associated with obesity, which is listed as a medical condition in this patient's chart. The patient denied the use of alcohol and collectively the two major causes of pancreatitis were ruled out. Idiopathic causes are always a possibility; however, since the patient was taking medications that have been linked to pancreatitis, this linkage was investigated as a potential cause.

A clinical review of the patient's chart and thorough literature search narrowed the list of drugs highly linked to pancreatitis. The search revealed hydrochlorothiazide and benazepril as the two most likely to be associated with drug-induced pancreatitis. In addition to the hydrochlorothiazide found in the combination of hydrochlorothiazide and triamterene, the patient was taking several medications that could cause pancreatitis such as benazepril, hydrocodone, gabapentin, and sertraline.[4,7,17] Triamterene is a potassium-sparing, distal tubule diuretic that can be used in combination with hydrochlorothiazide for hypertension.[10] There are no data supporting triamterene as a causative agent in drug-induced pancreatitis. The patient is also taking benazepril 10mg daily to manage hypertension. Although this class of drugs has been linked to drug-induced pancreatitis, there has only been one report connected to benazepril.[18] Because of the patient's past medical history of uncontrolled hypertension, this drug was continued for the management of hypertension. The patient's pancreatitis improved throughout the continuation of benazepril, rendering it unlikely to be the offending agent. In addition, the discontinuation of two antihypertension drugs in a patient with uncontrolled hypertension would not have been ideal.

The precise mechanism by which hydrochlorothiazide causes pancreatitis is unknown; however, thiazides as a class are well known to increase serum triglycerides levels.[6] The patient's triglyceride level was slightly elevated at 152mg/dL, and hypertriglyceridemia was ruled out as a primary cause. In some patients, thiazides have been documented to increase serum calcium and decrease serum phosphorus levels.[19] Alterations in calcium and phosphorus levels are also observed in hyperparathyroidism, and primary hyperparathyroidism is known to increase the risk of pancreatitis.[19] The patient's calcium level was obtained and was within normal limits, thus ruling out the possibility of hyperparathyroidism. Other information suggests that thiazides might act directly on the parathyroid or might affect both the parathyroid glands and the pancreas.[20] The thiazide dose usually associated with pancreatitis is >12.5mg per day.[21] The fact that the dose of hydrochlorothiazide was recently increased and no other changes to the patient are other medications was made, suggest that hydrochlorothiazide could be a potential caused.

The Naranjo algorithm[22] (Table 3) was employed to evaluate hydrochlorothiazide and benazepril as potential causes for an adverse drug reaction (ADR). The total score is a measure for the likelihood that the respective drug caused the ADR. Results indicate that hydrochlorothiazide and benazepril are both possible causes. The patient's condition improved while benazepril was continued throughout her hospital stay and after hydrochlorothiazide was discontinued, further supporting the possibility that the increased dose of hydrochlorothiazide before hospitalization as a possible link to the cause of the acute episode.

Table 3 Naranjo algorithm.[22]

Naranjo algorithm 22	Hydrochlorothiazide	Benazepril
Are there previous conclusive reports on this reaction?	1	1
Yes (+1) No (0) Do not know or not done (0)		
Did the adverse event appear after the suspected drug was given?	2	2
Yes (+2) No (-1) Do not know or not done (0)		
Did the adverse reaction improve when the drug was discontinued or a specific antagonist was given?	1	0
Yes (+1) No (0) Do not know or not done (0)		
Did the adverse reaction appear when the drug was read ministered?	0	0
Yes (+2) No (-2) Do not know or not done (0)		
Are there alternative causes that could have caused this reaction?	-1	-1
Yes (-1) No (+2) Do not know or not done (0)		
Did the reaction reappear when a placebo was given?	0	0
Yes (-1) No (+1) Do not know or not done (0)		

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DOI: 10.15406/mojph.2016.04.00075

Table continued...

Naranjo algorithm 22	Hydrochlorothiazide	Benazepril
Was the drug detected in any body fluid in toxic concentrations? Yes (+1) No (0) Do not know or not done (0)	0	0
Was the reaction more severe when the dose was increased, or less severe when the dose was decreased? Yes (+1) No (0) Do not know or not done (0)	0	0
Did the patient have a similar reaction to the same or similar drugs in any previous exposure? Yes (+1) No (0) Do not know or not done (0)	0	0
Was the adverse event confirmed by any objective evidence? Yes (+1) No (0) Do not know or not done (0)	1	0
Total Score >9=definite ADR; 5 to 8=probable ADR; 1 to 4=possible ADR; 0=doubtful	4	2

Limitations

Limitations were encountered in this case report. Although hydrochlorothiazide was discontinued, the drug was not reintroduced, thus only giving a possible link, but not final confirmation, that it was the drug that caused the pancreatitis. Additionally, this case was complex because the patient's past medical history was not significant for pancreatitis, however; there were risk factors associated with this disorder that are not discussed in this case report or documented in the patient's chart.

Conclusion

In a case of acute pancreatitis, where all other causes were ruled out, and increase in dose of hydrochlorothiazide was identified as the most likely possible cause of this drug-induced, acute pancreatitis disorder.

Acknowledgements

The author would like to the Ivan Portillo, M.L.I.S., and Pharmacy Librarian for his contributions to the literature search.

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