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Acute Pancreatitis Induced by Codeine: A Rare Case

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Abstract

Background: Acute pancreatitis caused by drugs is rare but clinically important. Among pain relievers, codeine has only occasionally been linked to this condition. Recognizing such cases can help physicians avoid misdiagnosis and prevent future attacks.

Case presentation: A 19-year-old man was admitted with sharp epigastric pain, nausea, and repeated vomiting. His serum amylase and lipase levels were high, and abdominal CT showed an enlarged pancreas with surrounding inflammation. The patient had been taking an acetaminophen–codeine combination regularly for headaches. There was no history of alcohol use, gallstones, elevated triglycerides, hypercalcemia, or a family tendency to pancreatic disease. Considering these findings, codeine-induced pancreatitis was the most reasonable diagnosis.

Conclusion: This case draws attention to codeine as a possible but uncommon cause of acute pancreatitis. It reminds clinicians to ask about opioid-containing drugs, especially in young adults who have used them for a long time and lack other risk factors.

Keywords: Pancreatitis, Analgesic opioid, Drug-Related Side Effects and Adverse Reactions, Case Reports.

1. Background

Acute pancreatitis (AP) is a common inflammatory condition of the pancreas with a broad clinical spectrum ranging from mild to life-threatening presentation that may end in organ failure. The incidence of acute pancreatitis is estimated at 10–20 cases per 100,000 population per year and remains associated with an inordinately high fatality rate in severe cases (1).

Gallstones and alcohol consumption cause the majority of acute pancreatitis (AP) episodes, and other etiologic agents, infection, trauma, and drugs, occur at significantly lesser frequencies. Drug-induced pancreatitis (DIP) contributes to approximately 0.1–2% of all episodes and is often diagnosed by exclusion (2). Over 130 drugs have been implicated, including Azathioprine, valproic acid, corticosteroids, and several opioid analgesics (1).

Codeine, an opioid painkiller, is widely used in combination with acetaminophen for pain relief. It is metabolically converted in the liver to morphine through the cytochrome P450 2D6 pathway. Administration of opioids has the potential to increase pressure in the pancreatic duct through spasms of the sphincter of Oddi, and this may cause obstruction and subsequent inflammation of the pancreas (3,4). Despite this mechanism, reports of codeine- induced pancreatitis remain uncommon, and only a few such cases

have been described in the published literature (2,4).

We present a 19-year-old man who acquired acute pancreatitis after long-term use of an acetaminophen–codeine combination product. This case illustrates an unusual etiology that clinicians should keep in mind when assessing patients with unexplained pancreatitis.

2. Case Presentation

2.1. Case Presentation

A 19-year-old man presented to our hospital with a four-day history of epigastric pain. The pain radiated to his back, was exacerbated by positional changes, and was associated with nausea and vomiting. Physical examination revealed tenderness, guarding, and rebound tenderness in the epigastric region. The patient denied any associated symptoms, including weight loss, steatorrhea, chronic biliary pain, or chronic abdominal pain, particularly postprandial pain. The patient had no history of alcohol consumption, gallstones, or hypertriglyceridemia. A comprehensive differential diagnosis was conducted, considering a range of conditions, including cholecystitis, peptic ulcer disease, and bowel obstruction, all of which were subsequently ruled out. Notably, the patient reported a similar, though less severe, episode of epigastric pain approximately 40 days prior. This earlier episode was managed on an outpatient basis with proton pump inhibitors (PPIs), clidinium C, and magnesium hydroxide, resulting in an improvement of pain within 2-3 days. Following this improvement, the patient developed a severe sense of postprandial fullness and an exaggerated gag reflex.

The patient's medication history included creatine, fluoxetine, propranolol, and acetaminophen codeine combination (four tablets daily for the preceding eight months). He reported a history of seasonal allergies but denied any known drug or food allergies. His family history was significant for ulcerative colitis, hyperlipidemia (HLP), and diabetes mellitus (DM). Laboratory tests showed leukocytosis (12,000/µL), elevated amylase (245 U/L), elevated lipase (80 U/L), and elevated lactate dehydrogenase (698 IU/L). All other serum levels were within normal limits. Abdominal ultrasound demonstrated edema and heterogeneity of the pancreatic tissue, surrounding inflammatory changes, and a moderate amount of retroperitoneal fluid. A computed tomography (CT) scan of the abdomen and pelvis, performed with and without contrast, confirmed the ultrasound findings, revealing peripancreatic swelling and inflammation.

2.2. Management

The patient was kept on bowel rest and was NPO (nothing by mouth). An NG (nasogastric) tube was initially inserted. Fluid therapy with isotonic saline was initiated to receive a urine output of 0.5 ml/kg/hr. He was administered 3 liters of normal saline at diagnosis, followed by maintenance IV fluids. For pain control, the patient received Pethidine 50 mg every 8 hours for 2 days and diclofenac 100 mg every 12 hours for additional pain relief. He was also given Optalgin 1 g every 12 hours and Pantoprazole 40 mg every 12 hours. After 48 hours of monitoring, the patient's condition improved. The patient's vital signs and abdominal findings were checked every 8 hours. Over the following days, progressive improvement was observed, with abnormal pain guarding, rebound tenderness, and overall abdominal tenderness decreasing. At this point, Pethidine was changed to PRN (as needed), and Optalgin was discontinued. Once the patient was allowed to resume oral intake, the NG tube was removed, and an advanced oral regimen was initiated.

Serum amylase and lipase levels declined steadily during hospitalization, and liver function remained within normal limits.

Following treatment, we recommended an outpatient follow-up for a psychological consultation, explicitly focusing on drug use and potential toxicity.

3. Discussion

This report describes a 19-year-old man diagnosed with drug-induced acute pancreatitis. Drug-induced acute pancreatitis (AP) is rare, but should always be considered in idiopathic presentations(2). Certain groups, including children, women, the elderly, and patients with advanced HIV infection or inflammatory bowel disease, may be at higher risk (5). However, our patient was a young man. Acute pancreatitis constitutes a real medical emergency.

Overall, various mechanisms may involve ductal obstruction, cytotoxic or metabolic injury, accumulation of a toxic metabolite or intermediate, and hypersensitivity reactions (2,5). Among implicated drugs, opioids such as codeine can cause spasms of the sphincter of Oddi, leading to increased pancreatic duct pressure and inflammation. Despite this evidence, there are no documented incidences of opiate-induced sphincter of Oddi spasm leading to pancreatitis (1,4).

The primary symptom is abdominal discomfort that arises in the epigastric and peri-umbilical regions, spreading to the right upper quadrant, and often radiates to the back and chest (6). The pain is usually more intense in the supine position and is relieved by sitting with the chest bent forward and the knees bent (7). This condition may also be accompanied by significant emesis, nausea, and abdominal distension associated with gastrointestinal hypomotility and chemical peritonitis (6, 7). The vomiting seen in acute pancreatitis is distinct from that caused by gastric issues, as it does not alleviate the abdominal pain and may even worsen it. Although the abdominal pain is intense, only 30% of patients exhibit a defense mechanism and muscle rigidity when their abdomen is palpated; our patient was experiencing severe epigastric pain along with nausea and vomiting (8).

Acute pancreatitis induced by drugs presents challenges for healthcare professionals for several reasons: 1) Many implicated medications lack sufficient diagnostic criteria; 2) it rarely presents with clinical or laboratory signs of a drug reaction, such as rash, lymphadenopathy, or eosinophilia; 3) a positive re-challenge, while supportive, is not definitive (2, 5).

In earlier years, specialists developed a classification system to evaluate the probability of specific medications being linked to acute pancreatitis. Codeine falls under class Ⅰ A, and our case indicates an abnormality associated with the use of this drug (Table 1) (5). Codeine is an opiate derivative acting as a partial agonist on μ, δ, and κ opiate receptors (9).

Table 1. Summary of drug-induced acute pancreatitis based on drug class: Badalov et al. (2) with modification

Class Ia	Class Ib	Class II	Class III	Class IV
Alpha-methyldopa	All-trans retinoic acid	Acetaminofen	Aledronate	Adrenocrticotrophic
Azodisalicylate	Amiodarone	Chlorthiazide	Atorvostatin	hormone
Benzafibrate	Azathioprine	Clozapine	Carmazepine	Ampicillin
Cannabis	Clomiphene	DDI	Captopril	Benzapril
Carbimazole	Dexamethasone	Erythromycin	Ceftriaxone	Betamethazone
Codeine	Ifosfamide	Estrogen	Chlorothalidone	Capecytabine

Cytosine arabinoside	Lynesterol/methoxyethinyl-estradiol	Lasparaginase	Cimetidine	Cisplatin
Dapsone	Lamivudine	Pegasparagase	Clarithromycin	Cyclophosphamide
Enalapril	Losartan	Propofol	Cyclosporin	Cyproheptidine
Furosemide	6-MP	Tamoxifen	Gold	Danazole
Isoniazid	Meglumine		Hydrochlorothiazide	Diazoxide
Mesalamine	Methimazole		Indomethacin	Doxorubicin
Metronidazole	Nelfinavir		Interferon/rivavirin	Famciclovir
Pentamidine	Norethindronate/mestranol		Irbesartan	5-fluorouracil
Pravastatin	Omeprazole		Isotretinoin	Fluvastatin
Procainamide	Premarin		Ketorolac	Lovastatin
Pyritonol	Sulfamethazole		Lisinopril	Octreotide
Simvastatin	Trimethoprim-sulfamethazole		Metalozone	Penicillin
Stibogluconate			Metalozone	Ranitidine
Sulfamethoxazole			Metformin	Rifampin
Sulindac			Minocycline	
Tetracycline			Mirtazapine	
Valproic acid			Paclitaxel	
			Predonisolone	

Several studies have pinpointed different medications as triggers for pancreatitis. An Australian study of 328 patients with acute pancreatitis found that 11 (3.4%) were induced by drugs. Codeine accounted for five of these cases (45%). In the cases identified as secondary to codeine, the average age of the patients was 40.6 years, and they had been consuming codeine for an average of 19.6 days (4,10). This patient was younger than the average age reported in the Australian study, and his pancreatitis duration was more prolonged.

The findings of the study by Hastier et al. which initially documented a set of four patients with pancreatitis induced by codeine in France. The average age of the patients was 50.2 years. Symptoms began an average of 1.1 hours after codeine consumption. All four patients received conservative treatment with intravenous fluid resuscitation and were discharged within one day of their admission. It was observed that three of the patients accidentally ingested codeine within a time frame of one week to three months after their admission, resulting in a recurrence of pancreatitis in all three cases, reinforcing the link between codeine and pancreatitis. Additionally, it was noted that all four patients had previously undergone cholecystectomy, suggesting that this could be a risk factor for codeine-induced pancreatitis (4).

The diagnosis of acute pancreatitis includes a significant rise in amylase levels within 12 hours of symptom onset, with a return to normal values of 300-700 IU/L (measured using the chromogenic assay) typically occurring within a few days of presentation; a notable increase in transaminase and lactic dehydrogenase levels, correlating with the degree of pancreatic cell necrosis; a considerable elevation in pancreatic lipase concentration, which often persists longer than the increase in amylase levels. Hematocrit levels may rise due to exudative effusion in the peritoneal cavity or decrease due to bleeding. Among

the most appropriate imaging studies, abdominal radiography without contrast for patients in both supine and upright positions is advised to rule out other acute abdominal issues, such as intestinal perforation or acute bowel obstruction (4,11). As mentioned in the case section, laboratory tests, elevated amylase, elevated lipase, elevated LDH, and ultrasound and CT scan confirmed acute pancreatitis.

In the majority of cases involving acute pancreatitis, the condition typically improves on its own, usually within 7 days after initiating pharmacological treatment, which includes analgesics (primarily non-steroidal anti-inflammatory drugs or NSAIDs); intravenous administration of fluids and colloidal solutions intended to preserve normal intravascular volume; and either parenteral or enteral nutrition (12). Antibiotic therapy was once routinely given to prevent septic complications linked to necrotic tissue (13). Studies have shown that the incidence of pancreatic infections does not diminish with prophylactic antibiotics (12). Consequently, it is recommended only to initiate antibiotic treatment if clinical assessments or laboratory tests (such as blood cultures) indicate ongoing sepsis (12).

4. Conclusion

If systemic medical treatment is ineffective, the subsequent most appropriate intervention is surgery. It involves the debridement of necrotic pancreatic tissue and the excision of retroperitoneal fluid, performed after the pancreatic structures have been isolated in the abdominal cavity and the peripancreatic fluid has been drained.

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