



## Codeine-Induced Pancreatitis in a Patient with Previous Cholecystectomy

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### Abstract

Codeine is a rare precipitant of acute pancreatitis. The hypothesised mechanism is transient codeine-induced sphincter of Oddi spasm. This case report describes an 80-year-old woman with previous cholecystectomy who developed acute pancreatitis within one hour after administration of a low dose (60 mg) codeine phosphate preparation for sialadenitis. The temporal profile, pathophysiology and management of codeine-induced pancreatitis are also reviewed.

### Keywords

Pancreatitis, Codeine, Opioids, Sphincter of Oddi dysfunction

### Introduction

Codeine may cause sphincter of Oddi dysfunction and is a rare precipitant of acute pancreatitis [1]. This case describes an elderly woman with previous cholecystectomy who developed acute pancreatitis after administration of a low dose codeine preparation for sialadenitis.

### Case Presentation

An 80-year-old woman was brought in by ambulance with acute onset epigastric pain. She had been reviewed in the Emergency Department the previous day for left submandibular sialadenitis and was discharged home on Augmentin duo forte and panadeine forte. Since discharge, she had taken one panadeine forte tablet (containing 500 mg paracetamol and 30 mg codeine phosphate) at 5.30 pm and a second tablet at 7.00 pm. Within an hour of taking the second dose of panadeine forte, she developed worsening epigastric pain radiating to the chest. The pain was aggravated by leaning forward and unrelated to exertion. She had associated nausea but no vomiting, dyspnoea or other associated symptoms. She denied any history of exertional chest pain or previous pancreatitis. Her co-morbid medical conditions included hypertension on ramipril, diet-controlled hypercholesterolaemia, previous laparoscopic cholecystectomy for biliary colic and hysterectomy. She denied any alcohol consumption or smoking and had no history of recurrent choledocholithiasis post-cholecystectomy.

On arrival in the Emergency Department, she was hyper-

tensive (blood pressure 199/112 mm Hg) but was otherwise haemodynamically normal with heart rate 67 beats per minute and temperature 36.8 degrees. On examination, her abdomen was soft with epigastric tenderness but no guarding or signs of peritonism. Bowel sounds were present. General examination was otherwise unremarkable. ECG and chest x-ray were normal. Laboratory indices included serum lipase 2578 U/L, amylase 692 U/L, white cell count  $11.3 \times 10^9/L$  and C-reactive protein 1.3 mg/L. Liver function tests were unremarkable (ALP 85 U/L, GGT 76 U/L, ALT 44 U/L, AST 83 U/L and bilirubin 5  $\mu\text{mol/L}$ ). Serial troponins and immunoglobulin G (IgG) subclasses were within normal limits (IgG1 7.78 g/L, IgG2 1.69 g/L, IgG3 0.21 g/L and IgG4 0.41 g/L).

The patient was admitted under the surgical team and managed conservatively with gut rest, intravenous fluids, antiemetics and analgesia. Her pain improved within 24 hours and diet was upgraded. Serum lipase had decreased to 200 U/L on day one post admission, white cell count had normalised ( $7.3 \times 10^9/L$ ) and C-reactive protein was 2.7. Her

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liver function tests however were deranged (ALP 112 U/L, GGT 200 U/L, ALT 325 U/L, AST haemolysed and bilirubin 7  $\mu\text{mol/L}$ ). She was discharged on day two with plan for outpatient CT cholangiogram. Her liver function tests were down trending on discharge (ALP 115 U/L, GGT 188U/L, ALT 231 U/L, AST 123 U/L and bilirubin 6  $\mu\text{mol/L}$ ).

## Discussion

Acute pancreatitis occurs most commonly secondary to gallstones (52%) or alcohol (28%) [1]. Drug-induced pancreatitis is a less common aetiology. It accounted for only 3.4% of cases in a 2011 Australian review of 328 cases of acute pancreatitis [1]. This included five cases of codeine-induced pancreatitis; with duration of codeine exposure ranging from one day to three months and a peak serum lipase of 2860. Only one patient had previously undergone cholecystectomy [1].

The hypothesised mechanism for codeine-induced pancreatitis is transient codeine-induced sphincter of Oddi spasm [1-3]. This has been shown to occur within five minutes of subcutaneous administration of codeine and may continue for over two hours [4]. In an experimental study by the Mayo Clinic in which 28 participants received subcutaneous injection of 130 mg codeine, seven patients had a subsequent increase in pancreatic enzymes and several patients experienced transient epigastric pain [5]. A significant transient increase in liver enzymes (particularly transaminases) is also common [5]. Spasm may involve the biliary segment of the sphincter (surrounding the distal common bile duct), pancreatic segment of the sphincter (surrounding the distal pancreatic duct) or both [6]. Biliary segment involvement presents with biliary-type epigastric or right upper quadrant pain that mimics biliary colic but is not postprandial [6]. Pancreatic segment involvement produces acute pancreatitis [6]. It is likely that the patient described in this case had involvement of both segments of the sphincter of Oddi or the distal part of the sphincter surrounding the ampulla of Vater.

The dose of codeine precipitating pancreatitis is variable however the majority of cases described in the literature occurred after a single low dose. Turkmen, et al. report the case of a 68-year-old gentleman with prior cholecystectomy who developed symptoms of pancreatitis (with serum lipase 234 U/L) 60 minutes after taking a single dose of 30 mg codeine combined with 300 mg paracetamol for viral myalgia. His symptoms resolved and serum lipase normalised after 48 hours of conservative management [2].

Torres, et al. describe a similar case of a 76-year-old gentleman with previous cholecystectomy who developed epigastric pain approximately one hour after taking 30 mg of codeine with 500 mg paracetamol for renal lithiasis. Serum

lipase was 155 U/L and his symptoms resolved within three hours with normalisation of serum lipase within one day [3].

Hastier also presents a case series of four patients who developed symptoms of pancreatitis within one to three hours of ingesting a therapeutic dose of codeine. Dose of codeine administered ranged from 40 mg to 60 mg. All patients had previously undergone cholecystectomy. One patient had serum lipase as high as 8417 U/L after taking 60 mg of codeine and took six days to recover [7].

Prior cholecystectomy is hypothesised to be a significant risk factor for codeine-induced pancreatitis. It is proposed that in the absence of the gallbladder as a reservoir, codeine-induced sphincter of Oddi spasm or constriction leads to increased pressure within the common bile duct and thus predisposes to pancreatitis [2,8]. It is also suggested that damage to the nerve fibres passing between the gallbladder and sphincter of Oddi during cholecystectomy may alter sphincter function [2]. Fibrosis or smooth muscle hyperplasia may also lead to stenosis and increased sphincter of Oddi pressure in approximately 60% of patients post-cholecystectomy [3,8]. Although most cases described in the literature occur in cholecystectomised patients, Obeid, et al. also report a mild case of acute pancreatitis (serum amylase 395 U/L) in a patient without prior cholecystectomy [9].

Management of codeine-induced pancreatitis is as per any other cause of pancreatitis with cessation of the codeine. Studies have also shown that the calcium channel blocker, Nifedipine, may reverse the effect of opiates on the Sphincter of Oddi [6]. As observed in the above case and in the literature, symptoms typically occur around one hour after administration of codeine and resolve within 48 hours of conservative management including cessation of codeine. Serum lipase derangement may range from mild (100-200 U/L) to severe (over 2000 U/L in this case). It is important to exclude more common aetiologies of pancreatitis including gallstones, alcohol-induced, hyper triglyceridaemia-induced and autoimmune pancreatitis. A pitfall in the investigation of this patient is that she did not undergo imaging to exclude gallstones or testing of triglyceride level. However, the patient's initial liver function tests were not suggestive of biliary obstruction and her history of hypercholesterolaemia controlled without the need for medication makes hypercholesterolaemia-induced pancreatitis unlikely. Furthermore, the temporal profile of her symptom onset, transient transaminitis and clinical improvement following cessation of codeine were highly consistent with codeine-induced pancreatitis as described in the literature. Autoimmune pancreatitis is another important differential diagnosis in this case as immunoglobulin G4-related pancreatitis may be accompanied by extra-pancreatic autoim-

mune phenomena including sclerosing sialadenitis, sclerosing cholangitis and retroperitoneal fibrosis [10]. However the patient was demonstrated to have normal IgG4 levels. Furthermore, glucocorticoid therapy is required to induce remission of autoimmune pancreatitis [10].

Overall, codeine-induced pancreatitis is a rare entity that may be precipitated by a single low dose of codeine and is typically characterised by acute onset of symptoms within one hour of codeine administration and resolution of pancreatitis within 48 hours. This phenomenon is likely to be under-reported. Clinicians should consider avoiding codeine preparations in patients with prior cholecystectomy to prevent this rare but potential risk.

### Conflict of Interest

None declared.

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