

## **Codeine Induced Pancreatitis: Something for all Clinicians to Consider**

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### **Abstract**

Pancreatitis is a relatively common cause of presentations to the Emergency Department, with gallstone disease and excessive alcohol intake being the predominant causative factors. Whilst Sphincter of Oddi dysfunction is the presumed mechanism, leading to reflux of pancreatic enzymes, the pathophysiology is not entirely understood, and there are a number of other known triggers, most notably, drug-induced. A case of a 16 year old man who developed acute pancreatitis shortly after first time ingestion of codeine is discussed herein.

**Keywords:** Codeine; Pancreatitis

### **Introduction**

Pancreatitis is a relatively common surgical presentation, and whilst there is an array of pathophysiological causes for acute pancreatitis, the most prevalent, particularly within the Western world, are biliary (cholelithiasis) and alcohol intake which account for over 80% of cases [1]. However, when assessing patients, particularly within an acute setting, one must be aware of the vast array of conditions that may be the causative factor of the patient's acute pancreatitis. Rare causes such as mumps and scorpion sting are more of a textbook diagnosis, and we are becoming more aware of autoimmune conditions. However, as we move into the 21<sup>st</sup> century where more of our patients are on a multitude of medications, we need, as clinicians, to be more aware of drug induced pancreatitis [2].

A diagnosis of acute pancreatitis requires two out of three criteria - epigastric pain, a raised serum lipase or amylase greater than three times the normal limit, and imaging features consistent with pancreatitis, namely peri-pancreatic oedema and swelling on computed tomography (CT) scan [3]. However, current belief is that radiological changes do not appear until at least 72 hours post onset of symptoms [3,4]. There are numerous scoring criteria available, looking at biochemical results, to predict the severity of the episode, including the patient's oxygenation levels (pancreatitis is known to precipitate Acute Respiratory Distress Syndrome [ARDS]), white cell count, liver enzymes, glucose, calcium, renal function and patient age. Particularly in an undifferentiated episode of acute pancreatitis, current guidelines are to acquire an abdominal ultrasound scan in the emergency setting, in order to determine the presence of gallstones and any subsequent biliary dilation, suggestive of passage of stone into the common bile duct (CBD) [1-4].

At present, there is currently no curative management, with correction of the underlying cause and supportive care as the fundamental aspects of treatment. Current guidelines suggest high flow oxygen, analgesia and intravenous fluid resuscitation. Early cholecystectomy for those with biliary pathology is often considered appropriate, whereas education to patients with alcohol induced pancreatitis regarding the sequelae of long-term complications is often beneficial [1,4].

The pathophysiology of cholelithiasis as a causative factor of acute pancreatitis is well understood, with transient blockage of the biliary system causing blockage of the ampulla of Vater, and subsequent reflux of the pancreatic enzymes. This in turn results in an increased activation of the enzymes that leads to an inflammatory response from the pancreas – pancreatitis [1,2,4]. In contrast, the exact mechanism by which alcohol causes pancreatitis still remains unclear. Initial belief was that it triggered spasm of the sphincter of Oddi with resultant reflux of pancreatic enzymes, followed by the theory of a “Ductal-Plug” by Sarles, *et al.* [5], which postulated that alcoholics are more likely to produce protein rich pancreatic juice, which in turn can block the pancreatic duct leading to acinar atrophy [6]. However, current research believes that excessive alcohol consumption interferes with cell signalling and that due to the pancreas being closely related to the liver in a developmental sense, the pancreas is capable of metabolising alcohol. Alcohol is metabolised in the liver by both oxidative and non-oxidative metabolism, with the resultant by-products having deleterious effects on the pancreas at a cellular level [7,8]. However, the causative effect of drug-induced pancreatitis, in particular codeine, is still relatively misunderstood, largely due to few cases being recorded in the literature, with spasm of the sphincter of Oddi thought largely to be the presumed mechanism [9].

A 16 year old Muslim male of African descent presented to the Emergency Department of a large tertiary hospital with a two day history of worsening pain of a left upper molar. His blood tests were unremarkable, with a white cell count (WCC) of  $6.45 \times 10^9/L$  (reference range  $4.00-11.00 \times 10^9/L$ ) and a lipase of 18 U/L ( $< 60$  U/L). He was referred to an outpatient dentist and prescribed paracetamol 1g + codeine 60mg as required, every 4 - 6 hours. The patient took one dose of the prescribed medication approximately 90 minutes following discharge from the Emergency Department. Within two hours, he developed sudden onset, sharp, severe epigastric pain radiating through to between his shoulder blades. He had associated nausea and diaphoresis, however remained systemically well. He had not consumed any diet since his initial presentation and ingestion of the medication. The patient reported no previous episodes of the pain and had no significant past medical history. He had no regular medications and had never previously taken codeine. He reported no alcohol intake secondary to his religion. He re-presented to the same Emergency Department and was found to be afebrile and haemodynamically stable, however examination of his abdomen revealed focal tenderness of the epigastric region without peritonitis. Repeat blood tests were unremarkable, about from a lipase of 487 U/L. A chest x-ray was performed, which revealed no adverse features and an abominable ultrasound scan revealed no cholelithiasis, the common bile duct was of normal size and calibre, nor was there any intra or extrahepatic dilatation. He was admitted to the Acute Surgical Unit and managed with vigorous intravenous fluid resuscitation and commenced on a proton pump inhibitor (PPI). He was kept nil by mouth overnight. His pain had markedly improved the following morning, and, once he had tolerated diet without resultant pain, he was discharged with a one week course of PPI therapy. The patient was advised to avoid codeine for the remainder of his life. Given the rapid resolution of symptoms, an autoimmune screen was not performed, and it was determined that his acute pancreatitis was secondary to recent, first time codeine ingestion.

There have been numerous studies that have identified various drugs as the causative agent for pancreatitis, with a single-centre trial out of Australia with 328 patients who presented with an acute episode, reporting that 11 of the cases (3.4%), were drug induced [10]. Codeine was found to be responsible for five of these cases (45%) - azathioprine was responsible for two cases, and one each for chlorothiazide, sodium valproate, oestradiol and rosuvastatin induced pancreatitis. In the cases deemed secondary to codeine, the average patient age was 40.6, whilst the average length of duration of codeine ingestion was 19.6 days. However, one of these patients had been taking codeine regularly for three months and had an overdose (amount not recorded) on the day of presentation. If this patient is excluded from results, the average duration of ingestion was two days. The mean peak lipase level was 1,439 U/L and the mean duration of stay was three days [10]. These results are similar to a retrospective paper by Hastier, *et al.* [9] which first reported a series of four cases of codeine induced pancreatitis in France. The mean age of patients was 50.2 years, and three of the cases were female. The average time before the onset of symptoms following codeine ingestion was 1.6 hours. All four patients were managed conservatively with intravenous fluid resuscitation and all were discharged within 6 days of admission. It was noted that in three of the patients there was a subsequent unintentional ingestion of codeine ranging from one week to six months post admission, with a recurrence of pancreatitis developing

in all three, thus strengthening the causality of codeine induced pancreatitis. It was noted that all four of these patients had had a prior cholecystectomy, suggestive that this was a predisposition to codeine induced pancreatitis [9]. This is supported by a case report by Turkmen, *et al.* [11] which reports a 68 year old man presenting to the Emergency Department with sudden onset epigastric pain and vomiting, 60 minutes after taking the first dose of 300mg acetaminophen + 30mg codeine prescribed by his family physician after experiencing symptoms consistent with a common cold. He was noted to have undergone cholecystectomy 35 years prior. The authors postulate that prior cholecystectomy predisposes to codeine induced pancreatitis in that, following the presumed spasm of the sphincter of Oddi post codeine ingestion, due to the lack of the reservoir capacity of a gallbladder, introduction pressure is increased with subsequent reflux of pancreatic enzymes [11].

### Conclusion

The majority of cases of acute pancreatitis can be explained by either gallstones or alcohol toxicity, and clinicians should suspect these in all patients presenting with epigastric pain and a subsequently raised lipase. However, it is important that a comprehensive history, in particular, a medication and drug history is obtained, because as shown, although rare, codeine induced pancreatitis has been identified as an acute cause, particularly in patients who have undergone prior cholecystectomy. Whilst the cases identified have all made a full recovery, all patients who present with acute pancreatitis following codeine ingestion should be advised to abstain from codeine for the duration of their lives. Further investigations and research needs to be undertaken into the pathophysiology of pancreatitis overall, in order to develop appropriate investigation and treatment regimes for affected patients.

### Bibliography

1. Nesvaderani M, *et al.* "Epidemiology, aetiology and outcomes of acute pancreatitis: a retrospective cohort study". *International Journal of Surgery* 23 (2015): 68-74.
2. Lerch M and Gorelick F. "Models of acute and chronic pancreatitis". *Gastroenterology* 144 (2013): 1180-1193.
3. Bollen T. "Acute pancreatitis: international classification and nomenclature". *Clinical Radiology* 71 (2016): 121-133.
4. Carroll J, *et al.* "Acute pancreatitis: diagnosis, prognosis and treatment". *American Family Physician* 10 (2007): 1514-1520.
5. Sarles H. "Alcoholism and pancreatitis". *Scandinavian Journal of Gastroenterology* 6 (1971): 193-198.
6. Chowdhury P and Gupta P. "Pathophysiology of alcoholic pancreatitis: an overview". *World Journal of Gastroenterology* 12 (2006): 7421-7427.
7. Clemens D, *et al.* "Alcoholic pancreatitis: new insights into the pathogens is and treatment". *World Journal of Gastrointestinal Pathophysiology* 7 (2016): 48-58.
8. Apte M, *et al.* "Alcohol and the pancreas [internet]". American Pancreatic Association (2016).
9. Hastier P, *et al.* "A new source of drug-induced acute pancreatitis: codeine". *The American Journal of Gastroenterology* 95 (2000): 3295-3298.
10. Barreto S, *et al.* "Drug-induced acute pancreatitis in a cohort of 328 patients. A single-centre experience from Australia". *Journal of the Pancreas* 12 (2011): 581-585.
11. Turkmen S, *et al.* "Prior cholecystectomy predisposes to acute pancreatitis in codeine-prescribed patients". *International Journal of Critical Illness and Injury Science* 5 (2015): 114-115.

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