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Case Report

Codeine: An Under-Recognized and Easily Treated Cause of Acute Abdominal Pain☆

Abstract

We present 2 cases of acute abdominal pain secondary to oral codeine that resolved after the administration of intravenous naloxone.

Codeine is a well-recognized but underappreciated cause of acute severe abdominal pain mediated through sphincter of Oddi spasm. It is thought to be of particular significance in patients who have previously undergone cholecystectomy. Administration of naloxone in low doses carries little risk and has the potential to be both diagnostic and therapeutic. Early recognition and management of this treatable condition has the potential to reduce unnecessary investigations and prevent possible progression to pancreatitis.

An 86-year-old man presented to the emergency department (ED) after referral from radiology. His general practitioner had requested a lumbar spine x-ray to investigate atraumatic lower back pain; this x-ray identified a wedge fracture at L1. He was given 1 g paracetamol and 60 mg codeine orally on his arrival in the ED at 2:25 PM.

His previous medical history included myocardial infarction and benign prostatic hypertrophy. He did not take any regular analgesia. He described an allergy to morphine, stating that it had "caused a heart attack." He was unable to elaborate any further on this, and no record of the issue was evident within local hospital records.

On initial assessment, he appeared comfortable at rest and looked well. His mobility was severely limited by lower back pain. His abdomen was soft and nontender with no palpable abdominal aortic aneurysm or flank tenderness. His physiologic observations were within normal limits. Neurologic examination was unremarkable, and digital rectal examination demonstrated normal perianal sensation and anal tone.

A computed tomography scan of his lumbar spine revealed an anterior loss of height at L1 with normal height posteriorly and no retropulsion of fragments into the spinal canal. There was no soft tissue swelling around the fracture, and appearances were in keeping with osteoporotic collapse. His aorta was also noted to be of normal caliber with no increase in retroperitoneal density.

The patient was noted to be in asymptomatic urinary retention, and a urinary catheter was inserted. Urinalysis was positive for nitrites, but subsequent urine culture was negative.

The patient developed severe epigastric pain and felt unwell while being reviewed by the orthopedic team. He became gray and diaphoretic; his blood pressure dropped from 161/74 to 91/48 mm Hg. His abdomen was soft with mild epigastric tenderness. A venous blood gas was unremarkable. A 12-lead electrocardiogram demonstrated first-degree heart block but no evidence of ischemia. Baseline bloods (full blood count, urea and electrolytes, liver function tests, amylase, coagulation screen, and a group and save) taken after the onset of abdominal pain demonstrated a marginally elevated bilirubin of 24 μmol/L (reference range, 0-21μmol/L) and a mild thrombocytopenia; they were otherwise unremarkable.

Given his previous reaction to morphine and the otherwise unexpected development of abdominal pain, it was hypothesized that this patient's symptoms were related to codeine administration. Naloxone 400 mcg was administered intravenously at 5:25 PM, and the patient's abdominal pain resolved within 10 minutes. His physiologic parameters also returned to baseline, and he felt systemically well. He required no further analgesia.

The orthopedic team felt that his lumbar spine fracture was likely to be old, and therefore, he was admitted under the urology team for investigation and management of his urinary retention. His abdominal pain did not recur, and he was discharged the next day after a successful trial without catheter.

A 67-year-old man with a background of diverticular disease and a previous laparoscopic cholecystectomy presented to the ED with sharp, cramping abdominal pain, worst in the epigastric region. It began 30 minutes after he took 30 mg of oral codeine; this had been prescribed earlier that day by his general practitioner to treat a 10-day history of mechanical-sounding lower back pain. Up until this point, the patient had been self-medicating with paracetamol and was opioid naive.

He arrived at the ED stating that he had "been poisoned." He had not vomited, and he had had a normal bowel movement that morning. He was feeling well before the onset of the abdominal pain. He had no other significant medical history, took no regular medication, and had no known drug allergies or intolerances.

On examination the patient's abdomen was soft and nontender with no palpable masses. He was hypertensive and tachypneic with a pulse rate of 90 beats per minute. Baseline bloods (including amylase) were unremarkable, and a urine dip was negative.

Twelve-lead electrocardiogram was unremarkable, and a bedside ultrasound scan demonstrated a normal caliber aorta.

Given the temporal association, it was hypothesized that the patient's abdominal pain may be secondary to the codeine. Naloxone 400 mcg was administered intravenously at 2:15 PM, and the patient was pain free by 2:30 PM. He was also given paracetamol 1 g intravenously during this period. His symptoms returned at 2:55 PM and responded well to a further dose of naloxone. The patient was discharged, pain free, at 4:56 PM.

Acute abdominal pain secondary to the administration of opioids, including morphine [1,2] and codeine [3], is relatively well documented in

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the literature; indeed, it is an identified side effect in the product literature [4]. However, little has been written on the topic in recent years. Sphincter of Oddi (SO) spasm is the frequently implicated mechanism [1,2,5]; considerable biologic plausibility exists for this hypothesis as opioid medications have been shown to increase common bile duct pressures [6] as well as causing functional biliary obstruction [7] and SO spasm [8]. This is a class effect of the opioids; multiple different medications have been implicated [6,9-11].

More recently, codeine is being recognized as a cause of both SO spasm [12] and acute pancreatitis [13-15]. Patients who have previously undergone a cholecystectomy would appear to be at greater risk, possibly because of the lack of reservoir capacity to accommodate transient SO spasm and subsequent increased biliary pressures [12,14]. It is hypothesized that pre-existing SO dysfunction secondary to the previous cholecystectomy may compound this problem [12,15].

Codeine is an analgesic in common use for the management of mild to moderate pain [16]. Usually taken orally, it is readily absorbed from the gastrointestinal tract; peak plasma levels are reached in approximately 1 hour [4]. Different theories exist regarding its mechanism of action. Classically, it has been thought that the conversion of codeine to morphine by the liver enzyme CYP2D6 has been responsible for its analgesic efficacy [17,18]; however, the proportion of the total dose of codeine converted to morphine is only 0.5%-3% [19,20]. Alternative explanations have therefore been sought; one potential mechanism is via glucuronidation by UGT2B7 to codeine-6-glucuronide [21], a compound thought to have analgesic effects [22].

CYP2D6 enzyme activity and, therefore, the metabolism of codeine to morphine are extremely variable between individuals. Some are ultrarapid metabolizers and will therefore rapidly convert oral codeine to morphine [23]. It has been proposed that patients who are rapid metabolizers are those at greatest risk of codeine-induced SO spasm [24].

Naloxone reduces common bile duct pressures when given after opioid administration [6]; as in the cases presented above, treatment with naloxone has also been shown to improve the symptoms of opioid-induced acute abdominal pain [1,2,5]. There is suggestion that it acts as a competitive antagonist in this situation [8].

Despite the widespread use of codeine, this potential side effect does not seem to be well appreciated by emergency physicians (or indeed the medical community in general). This case series and the other examples present in the literature may suggest that its scarcity is more a problem of under-recognition than a true representation of a low incidence.

Abdominal pain is a common presenting complaint in the ED but offers its own difficulties in assessment and management. A significant minority who are admitted to hospital for investigation subsequently have no diagnosis confirmed. A careful drug history is essential in assessing these patients, particularly in those with a previous cholecystectomy. Low-dose opiates (eg, co-codamol 8/500) are readily available without prescription in many countries, and it is possible that these may be overlooked both by the patient and the physician alike.

Opioid-induced SO spasm can lead to pancreatitis [13-15], a potentially life-threatening condition. Early recognition and treatment with naloxone will be both diagnostic and therapeutic and may prevent progression to pancreatitis. Naloxone is readily available in the ED and has few side effects, and prompt treatment may prevent multiple unnecessary investigations.

Codeine is a well recognized but underappreciated cause of acute abdominal pain mediated by SO spasm. The spasm can be sufficiently severe to cause presentation to the ED and can lead to pancreatitis. Patients with previous cholecystectomy seem to be at higher risk. We have experience of 2 patients whose symptoms have been relieved by the administration of naloxone. A careful drug history is important to ensure that this treatable condition is not missed and may reduce the number of cases progressing to pancreatitis.

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Andrew Tabner, BMedSci (Hons), BMBS, MCEM*
Graham Johnson, BMedSci (Hons), MB/ChB, FCEM
Emergency Department, Royal Derby Hospital, Derby DE22 3NE United Kingdom
*Corresponding author. Emergency Department, Royal Derby Hospital Uttoxeter Road, Derby DE22 3NE, United Kingdom
E-mail address: andrew.tabner@nhs.net

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