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Title:
Acute opioid withdrawal following administration of oral oxycodone–naloxone due to portosystemic shunts

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Abstract

Background

The management of pain in patients with advanced liver disease is a clinical challenge. Initial pharmacokinetic safety data advised against the use of oxycodone-naloxone in this population however, in clinical practice it is commonly used.

Aim

Our case aims to illustrate a potential mechanism by which administration of oxycodone-naloxone can cause systemic opioid antagonism and harm to patients.

Clinical details

A 45 year-old man received two separate doses of oxycodone-naloxone in the immediate post-operative setting resulting in symptoms and signs consistent with acute opioid withdrawal. A review of his imaging revealed significant portosystemic shunts.

Outcomes

Porto-systemic shunts in patients with advanced liver disease may lead to a decrease in the phase II hepatic metabolism of naloxone and increased systemic levels. In the case of someone with pre-existing opioid dependence this may precipitate acute opioid withdrawal.

Conclusion

The use of oxycodone-naloxone preparations should be avoided in patients with liver disease and portosystemic shunts.

Key Words

Adverse Effect

Analgesics

Clinical Pharmacokinetics

Liver

Prescribing Practices

Introduction

Pain management in patients with advanced liver disease can be clinically challenging. Adverse events from analgesics are frequent and there is a paucity of prospective studies to guide evidence based management [1].

Portosystemic collaterals are a common complication of advanced cirrhosis and their development is central to many of the complications of liver disease including hepatic encephalopathy, variceal bleeding and potentially drug metabolism [2].

Oxycodone-naloxone (Targin™, Mundipharma) is a combination medication commonly used in the post-operative setting for analgesia. It contains oxycodone, a full opioid receptor agonist whose principle action is analgesia, and naloxone a competitive opioid antagonist with extensive first pass hepatic metabolism which reduces opioid related constipation without a clinically significant systemic effect [3].

Pharmacokinetic safety studies have advised against the use of oxycodone-naloxone in patients with moderate to severe hepatic dysfunction due to an increase in observed serum concentrations of naloxone [4]. However, given the limited number of analgesics available for use in patients with advanced cirrhosis, oxycodone-naloxone continues to be used in clinical practice in this patient population.

Case Report

We report on a case of a 45 year-old man with Child Pugh B (score 9) cirrhosis secondary to previously treated hepatitis C virus infection. The patient presented for elective surgical repair of a paraumbilical hernia. The gentleman had a history of chronic lower back pain which was managed

in the community with a 25 mcg/hr fentanyl patch and oxycodone IR 20 mg as required. In addition to these analgesics his other regular medications included escitalopram 20 mg daily, rifaximin 550 mg twice daily, pantoprazole 40 mg daily, phytomenadione 10 mg daily and sulfamethoxazole/trimethoprim 800/160 mg daily.

The patient underwent an uncomplicated open repair of his umbilical hernia and was returned to the surgical ward. He was charted post-operative analgesia including sustained release oxycodone-naloxone 10 mg SR twice daily.

The first dose of oxycodone-naloxone SR was administered at 22:00 and at 00:15, the patient developed severe uncontrolled abdominal pain, tachycardia and diaphoresis. He was assessed by the medical emergency team and empirically commenced on intravenous antibiotics for possible spontaneous bacterial peritonitis and given a stat dose of oxycodone 10 mg. The patient's symptoms resolved by 0230.

On the following morning the patient received a second dose of oxycodone-naloxone SR at 08:02 and developed similar symptoms to the previous night approximately at 10:25. The symptoms were felt to be secondary to acute opioid withdrawal and were alleviated by administration of intravenous fentanyl totaling 100 mcg. The oxycodone-naloxone SR was discontinued at this time and the patient did not experience further events. Using an adverse drug reaction probability scale (Naranjo algorithm), the event was assessed as a probable adverse drug reaction (score of 8) [5].

Review of the patient's previous imaging demonstrated large lienorenal varices indicative of portosystemic shunts [image 1].

Discussion

Oral naloxone undergoes significant first pass metabolism and its oral bioavailability has been established as less than 3%, however previous safety and pharmacokinetic studies have demonstrated profoundly higher concentrations of naloxone in patients with moderate to severe hepatic impairment when compared to healthy subjects. The AUC of naloxone was increased by 11,000% in patients decompensated cirrhosis (Child Pugh scores of 10-15) compared with healthy subjects. However, there was no observed increase in adverse events in the patients with hepatic impairment [4].

Acute opioid withdrawal has previously been reported by Greene et al following both oral ingestion and intravenous injection of crushed tablets in patients with opioid dependence [6]. More recently, Hauser et al described multiple cases where administration of oxycodone-naloxone led to severe uncontrolled pain in patients with liver metastases, proposed to be secondary systemic opioid antagonism [7]. Acute withdrawal following intravenous injection of oxycodone/naloxone is a result of bypassing of first pass metabolism. However the mechanism by which increases in systemic naloxone concentration occur following oral ingestion, and by which opioid antagonism and subsequent withdrawal develops is not well established.

Naloxone is normally metabolised through a phase II conjugation reaction via glucoronidation to inactive compounds naloxone glucoronide and 6B naloxol, which are excreted in the urine. Although it is possible that this metabolic process is impaired in the setting of cirrhosis, studies suggest that drug conjugation in patients with mild to moderate liver disease, is generally only mildly impaired [8], which would not explain the dramatically increased concentrations observed in the original safety data. In our case we propose that portosystemic shunting in the presence of portal hypertension resulted in systemic absorption of naloxone that had not undergone first pass metabolism resulting in higher systemic concentrations of naloxone and acute opioid withdrawal.

We advise clinicians that this class of medications should be used with caution in patients with Child Pugh A cirrhosis and avoided in patients with Child Pugh B and C cirrhosis.

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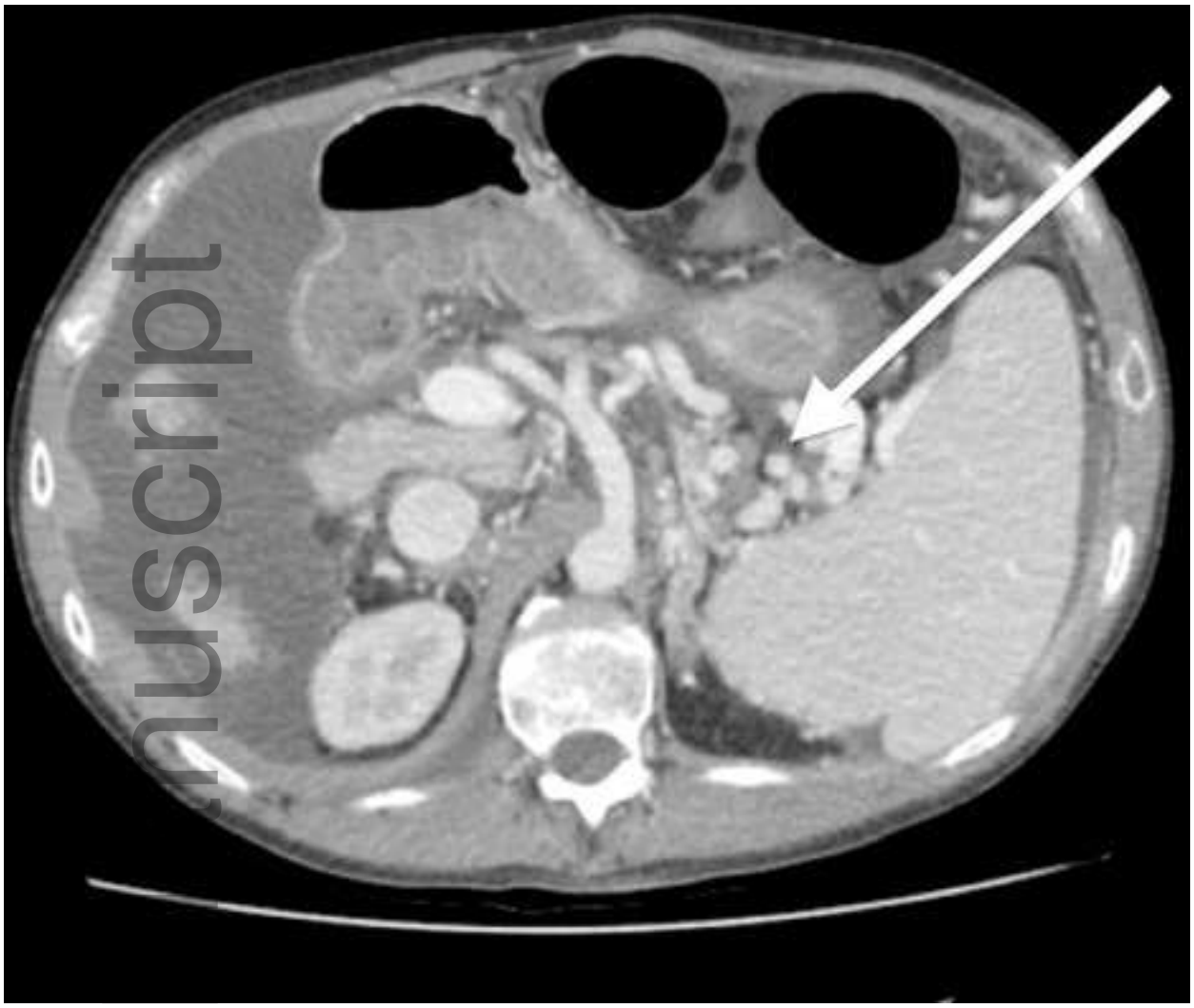

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