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The Curious Case of Opioid-Induced Pancreatitis

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Abstract: ***While most cases are known to be caused by gallstones or alcohol, a myriad of other causes have also been identified; medications being one of them. A wide array of medications have robustly been proven to cause pancreatitis [1] Opioid-induced pancreatitis, specifically, is less well documented. Only a handful of cases have been published, with Codeine being implicated as the trigger.[2–7] Interestingly, these Codeine pancreatitis cases are almost exclusively seen in post-cholecystectomy patients.[2–7] This is the case of a 54-year-old female presenting to the emergency department with acute-onset severe, crampy, epigastric pain, radiating to her back. The patient had accidentally ingested Acetaminophen with Codeine, thinking it was a sleeping aid. Approximately one hour after the ingestion, her symptoms began. The pathophysiology of opioid-induced pancreatitis is reviewed, with the proposed mechanism of codeine-induced Sphincter of Oddi spasm. In conclusion, opioid-induced acute pancreatitis in post-cholecystectomy patients has been well-established but surprisingly under-documented. There is tangible and pragmatic clinical importance, as clinicians should consider the increased risk of acute pancreatitis in patients with prior cholecystectomy, when prescribing opioid medications. Should a clinician find themselves with this patient presentation, naloxone seems to be an effective treatment, along with standard pancreatitis treatment, and discontinuation of the offending agent.***

I. INTRODUCTION

Acute pancreatitis is defined as a patient with at least two of the following findings: abdominal pain, elevated serum pancreatic enzymes at least three times the upper limit, and characteristic changes on imaging. While the most common cause of acute pancreatitis are gallstones or alcohol, a number of other causes have been identified including medications. Drug-induced pancreatitis is a well-known occurrence and a wide array of medications have been described in literature.[1] Opioid induced pancreatitis is less well documented and a literature search results in a handful of cases in which codeine has been implicated as the trigger.[2–7] This is a case of acute pancreatitis in a patient with prior cholecystectomy following the usage of codeine which was treated with opioid reversal with symptomatic relief.

II. CASE PRESENTATION

A 54-year-old female presented to the emergency department with acute onset severe crampy epigastric pain radiating to her back. The patient had accidentally ingested Acetaminophen with Codeine, thinking it was a sleeping aid. Approximately one hour after the ingestion, her symptoms began. She denied any associated nausea, vomiting, diarrhea or fevers. This was apparently not her first issue with Codeine, as she reported suffering from severe epigastric pain following Codeine ingestion several years prior. The patient was given Codeine postoperatively following an elective cholecystectomy for gallstones. She was treated with opioid reversal, which immediately relieved her symptoms. She reported that anesthesia informed her that this reaction was most likely due to her recent cholecystectomy, but was unable to remember how the physician made that connection. Over the course of several following years, she reported additional episodes of this pain after receiving Morphine and Dilaudid for various ailments. Her other medical history included insomnia, treated with over the counter sleeping-aids, and attention deficit hyperactivity disorder. She took no additional routine medications. There was no history of excessive usage of alcohol or trauma and her surgical history included the aforementioned cholecystectomy, hysterectomy, and most recently a lower extremity tendon lengthening procedure.

Physical examination revealed an afebrile, normotensive female without tachycardia. Abdominal exam revealed normoactive bowel sounds, without distension, however, she had significant epigastric tenderness without guarding, rebound, or peritoneal signs. EKG showed an incomplete left bundle branch block, otherwise unremarkable. Pertinent labs were significant for lipase 1787 U/L, AST 199 U/L, and ALT 102 U/L. ALP, bilirubin, remainder of electrolytes and complete blood count were all within normal limits otherwise. Follow-up CT imaging showed multiple hepatic cysts otherwise unremarkable without peripancreatic fat stranding, abscess, or biliary dilation. The patient received intravenous fluids and opioid reversal of 0.4mg naloxone IV while in the emergency department, with resolution of her symptoms, but was subsequently admitted for further management of her acute pancreatitis. During her admission, repeat blood work showed a marked improvement of her Lipase, down to 417 U/L, however, an upward trend in transaminases was seen. AST 994 U/L, and ALT 670 U/L, up from normal/high end normal upon admission. Viral hepatitis serologies were therefore obtained but found to be negative. The patient continued to clinically improve overnight and was discharged the following morning with primary care follow up.

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III. DISCUSSION

While codeine is a well-established cause of pancreatitis, only a handful of cases have been reported in literature.[2–7] Interestingly, they're almost exclusively seen in post-cholecystectomy patients.[2–7]

Pancreatitis-inducing drugs have been classified into four categories (I-IV) by Badalov. Class I drugs are defined as drugs in which there were at least 1 case report with positive rechallenge. Class Ia further includes the caveat that other causes of pancreatitis have been ruled out including alcohol, hypertriglyceridemia, gallstones and other drugs. Codeine is included in class Ia.[8]

The proposed mechanism of codeine-induced pancreatitis is sphincter of Oddi spasm. The sphincter of Oddi, which surrounds the confluence of the distal common bile duct and pancreatic duct, has been demonstrated to spasm in as little as five minutes following administration and lasting up to two hours.[9] Additionally, the effect of sphincter of Oddi dysfunction has been demonstrated with other opioids, including in Morphine in humans, as well as Meperidine, and Pentazocine in animal studies. These observations may actually serve as evidence implicating opioids as a spasm-inducing medication class.[10,11] This effect was further studied in patients using morphine by Helm et al, who found that both intraluminal pressures, spasm frequency, and amplitude were increased with morphine.[12] Studies of subcutaneous codeine injections have also demonstrated pancreatic enzyme elevations within two hours, with positive re-challenge occurring in one patient.[13] Transient elevations of transaminases were also documented.[11,13] With post-cholecystectomy patients, specifically, it is theorized that there is a lack of reservoir capacity, resulting in increased intraluminal pressure with sphincter spasm.[4] Alternatively, it is hypothesized that cholecystectomy results in damage to the nerve fibers controlling sphincter function, perhaps making them more sensitive to even a miniscule amount of spasm induction.[14]

Management of codeine-induced pancreatitis involves standard treatment of pancreatitis and discontinuation of the offending agent. As the class of opioids has been implicated in the development of sphincter of Oddi dysfunction and subsequent pancreatitis, one could infer that opioid reversal may be effective in treatment. In this case, a trial of naloxone 0.4mg was used with symptomatic resolution. Interestingly, in Helm's et al. study, naloxone was found to decrease spasm frequency and amplitude, however, the increased basal intraluminal pressure caused by morphine was unaffected. The possible implication is that perhaps opioids affect other receptors involving in spasming.[12]

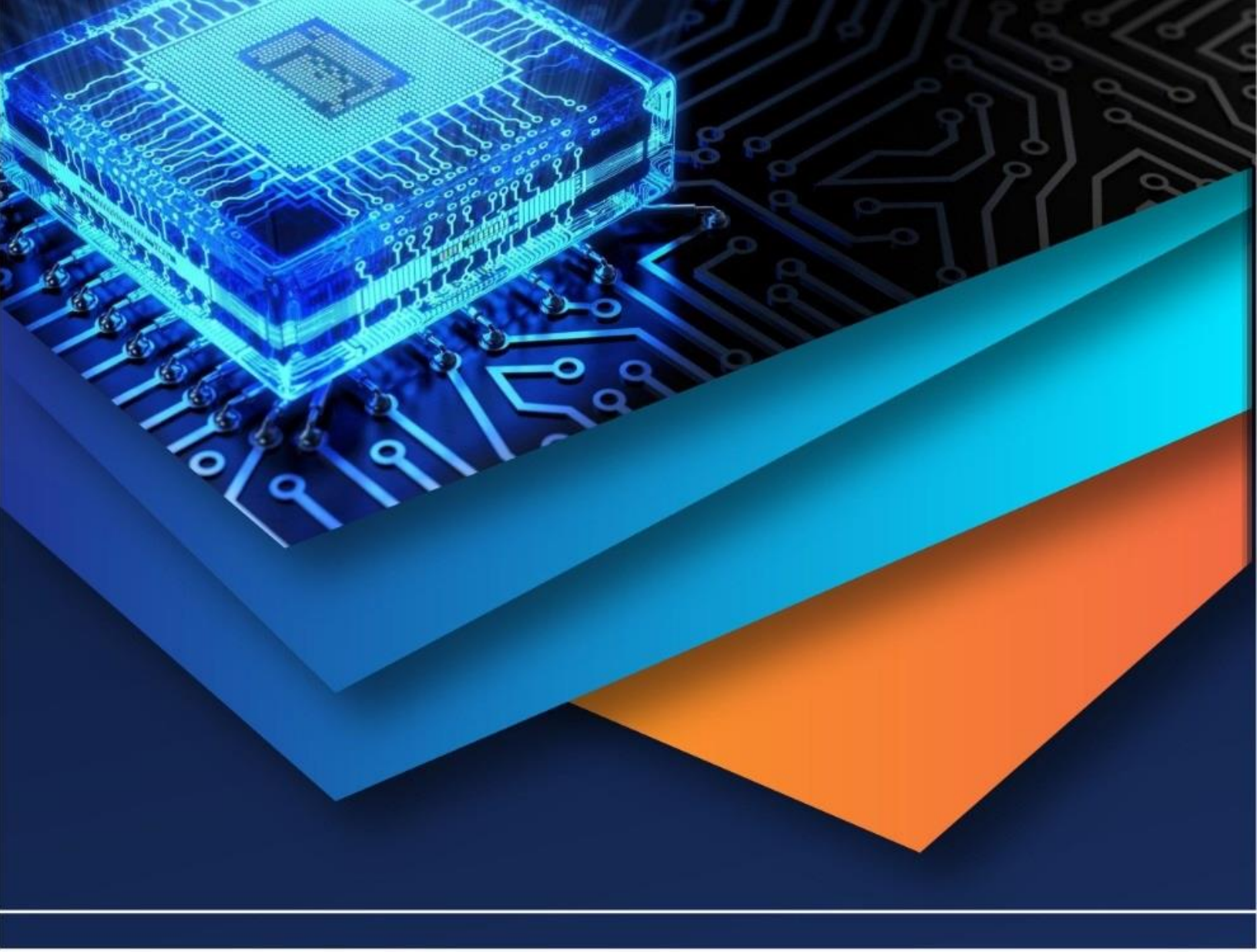
IV. CONCLUSION

In conclusion, opioid-induced acute pancreatitis in post-cholecystectomy patients has been well-established but surprisingly under-documented. There is tangible and pragmatic clinical importance, as clinicians should consider the increased risk of acute pancreatitis in patients with prior cholecystectomy, when prescribing opioid medications. Should a clinician find themselves with this patient presentation, naloxone seems to be an effective treatment, along with standard pancreatitis treatment, and discontinuation of the offending agent.

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