Metronidazole induced acute pancreatitis

Haroon Yousaf, Irfan Saddique

ABSTRACT

Introduction: Pancreatitis is a very rare adverse effect of metronidazole with only eight cases of metronidazole-induced pancreatitis reported so far. Case Report: A 23-year-old African-American female developed acute pancreatitis following treatment with metronidazole for vaginal trichomoniasis. She took metronidazole at two different times and experienced the severe epigastric pain and vomiting one hour after each dose. These episodes were unrelated to alcohol ingestion, gallbladder disease or other known causes of pancreatitis. Laboratory studies revealed elevated amylase and lipase concentrations and CT scan confirmed the findings consistent with acute pancreatitis. After discontinuation of metronidazole, the patient's abdominal pain improved, and both amylase and lipase concentrations immediately declined and were within normal limits after one day. Conclusion: High degree of suspicion is warranted on the part of physicians to diagnose metronidazole induced pancreatitis in patients presenting with gastrointestinal symptoms after metronidazole exposure. We suggest that metronidazole be discontinued when clinical or biochemical features of acute pancreatitis occur, once other known causes of pancreatitis have been excluded and rechallenge should be avoided.

Keywords: Pancreatitis, Metronidazole, Drug toxicity


INTRODUCTION

Metronidazole is a commonly used antibiotic agent in various conditions such as anaerobic bacterial infections, protozoa infections (for example, giardiasis), helicobacter associated gastritis and Crohn’s disease. The adverse side effects of metronidazole include gastrointestinal upset, metallic taste [7], urticaria [1], headache, peripheral neuropathy [7] and rarely pancreatitis.

Acute pancreatitis is an inflammatory disease with a wide spectrum of severity [11]. It is clinically characterized by acute constant abdominal pain [12] and elevated pancreatic enzymes [12]. Alcoholism and biliary tract stone disease account for 95% of cases [13].

Approximately 2% of pancreatitis in adults is drug induced [9, 14, 15]. Drug induced pancreatitis can occur in both children and adults [16, 17] with as many as 13% of paediatric cases of acute pancreatitis being due to medicines [16]. Time to onset can be six to nine months after commencement of the suspect causative medicine [16, 17].

Only eight cases of metronidazole induced pancreatitis have been reported in the English literature.

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so far [1–8]. The exact mechanism of action of metronidazole induced pancreatitis is unclear but a trigger role for the drug seems likely. This case report presents laboratory- and image-proven pancreatitis in a young female who took metronidazole on two different occasions and experienced the same epigastric symptoms one hour after each dose.

CASE REPORT

An otherwise healthy 23-year-old African-American female presented with complaints of severe epigastric pain, nausea and vomiting one hour after taking 1000 mg of metronidazole. Her primary care physician had prescribed the drug for symptomatic vaginal trichomoniasis one day prior to presentation. One hour after the first dose, the patient experienced severe epigastric pain with cramping that lasted 8–10 hrs. On the next day she took a second dose and had the same response, only without improvement. The patient had two episodes of vomiting and was unable to eat for 16 hours. Her doctor discontinued metronidazole by telephone and advised her to go to the nearest emergency room.

The patient had no other concurrent medications, previous surgical history or any history of alcohol use. She also denied trauma, weight loss and or family history of pancreatic disease.

Significant physical findings included only sinus tachycardia and moderate epigastric tenderness. There was no rigidity or guarding and bowel sounds were normal. There were no palpable abdominal masses. She had no fever or jaundice. Serum amylase was 327 IU/ml and serum lipase was 876 IU/ml. Abdominal ultrasound showed no evidence of gallstones. The common bile duct was of normal caliber and the pancreas were obscured by bowel gas. Abdominal computed tomography showed a mildly edematous, inflamed pancreas. Biliary and hepatic enzymes were normal. Serum calcium was 9.5 mg/dl, triglycerides were 121 mg/dl, glucose was 187 mg/dl, and the white blood cell count was 16.1×10³ cells/mm³ with 80% neutrophils. The remainder of the admission panel was normal.

Supportive management of IV fluid resuscitation, analgesia, antiemetic and nil per oral was instituted. The medical pain therapy was ordered with meperidine PCA and the pump was set to inject 5 mg/hour basal infusion, 5 mg bolus with a lockout time of 30 minutes. The next day meperidine was switched to oral oxycodone 10 mg every six hours. Her clinical course was uncomplicated and amylase returned to normal on day-2 post admission (Table 1). She began to tolerate light diet on day-2 and was discharged on day-3 on PRN (as needed) analgesics.

The patient had an outpatient follow up one month after discharge where she denied any vomiting and her abdominal pain was fully resolved.

DISCUSSION

The most common causes for pancreatitis in adults are cholelithiasis and excessive alcohol use, accounting for 35-40% and 30% of cases, respectively. Other causes include anatomic variants of pancreas, mechanical obstruction to pancreatic juice, hypertriglyceridemia, hypercalcemia, drug induced, toxins, trauma, ischemia, infections and autoimmune conditions [18]. Many medications also have been identified as a probable cause of acute pancreatitis. The first to report a case of drug-induced acute pancreatitis was Zion et al. in 1955; they described a case of hemorrhagic pancreatitis associated with cortisone therapy [19]. Drug-induced pancreatitis is rare, although more than 100 drugs have been implicated in causing this condition. It is rarely accompanied by clinical or laboratory evidence of a drug reaction, such as eosinophilia and rash [20].

![Figure 1: Abdominal ultrasound revealing normal gallbladder with no evidence of stones.](Image)

![Figure 2: Computerised tomography of abdomen on admission showing pancreatic inflammation.](Image)
association of drugs with acute pancreatitis include aminosalicylates, L-asparaginase, azathioprine, didanosine, estrogen, furosemide, pentamidine, sulfonamide, tetracycline, thiazides, valproic acid, vinca alkaloids and 6-mercaptopurine [18].

A detailed history and physical examination along with routine radiological evaluation consisting of ultrasound and/or CT of the abdomen can detect the underlying etiology of acute pancreatitis in approximately 80% of patients. If this initial investigation is unrevealing, the patient is classified as having idiopathic acute pancreatitis [21].

Mallory et al. in 1980 proposed criteria for classifying drugs as having an association with pancreatitis [10]:
1. pancreatitis develops during treatment with the drug;
2. other likely causes of pancreatitis are not present;
3. pancreatitis resolves upon discontinuing the drug;
4. pancreatitis usually recurs upon readministration of the drug.

Drugs are classified as having either a definite, probable or possible association with pancreatitis based on the degree to which these criteria are met. Proving a definite association requires that all the criteria mentioned above are met. An association is considered as probable if some but not all of the above mentioned criteria are met.

Only eight cases of metronidazole induced pancreatitis are described in literature [1–8]. All the cases were reported in females and led to a rapid recovery with supportive measures and discontinuation of the drug. In five patients, the pancreatitis recurred at least once on rechallenge with the drug, which lends validity to the possible causality of the reaction.

One case report describes a 23-year-old woman who developed pancreatitis on three separate occasions after being treated with metronidazole for Gardnerella vaginitis; her symptoms began 3-7 days after she started taking the drug [2]. Another report describes a 22-year-old woman who was treated with metronidazole for a vaginal infection and developed pancreatitis within 12-24 hours after taking the first dose [3]. She was rechallenged inadvertently two more times; pancreatitis occurred with each episode. Three episodes of acute pancreatitis associated with metronidazole occurred in a 45-year-old woman [4]. A 29-year-old woman developed pancreatitis on two separate occasions while taking metronidazole for the treatment of postpartum vaginal discharge [5]. The repetitious aspect of this adverse reaction confirmed the causality of the reaction. This characteristic establishes a strong link between metronidazole and this adverse effect, although reports have been rare. Patients in the remaining case reports were not rechallenged with the drug [6, 7].

Metronidazole is reported as having a probable association with acute pancreatitis, although the mechanism of drug-induced pancreatitis is not known. One speculative mechanism of metronidazole-induced pancreatitis is that, under aerobic conditions, metronidazole may undergo redox cycling and yield hydrogen peroxide, superoxide and other free radicals [22]. Such redox-active compounds are toxic to pancreatic beta-cells and oxygen-centered free radicals have been implicated in the induction of pancreatitis. Other suggested mechanisms include immune-mediated inflammatory response, pancreatic duct constriction, and metabolic effects [23].
Hence it is important to consider metronidazole as a possible etiology for acute pancreatitis in patients presenting with pancreatitis even after a few days of metronidazole exposure.

CONCLUSION

This case shows that clinicians should strongly consider discontinuing metronidazole in patients with pancreatitis of no identifiable source.

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Author Contributions

Haroon Yousaf – Substantial contributions to conception and design, acquisition of data, Drafting the article, revising it critically for important intellectual content, Final approval of the version to be published

Irfan Saddique – Substantial contributions to conception and design, analysis and interpretation of data, Drafting the article, revising it critically for important intellectual content, Final approval of the version to be published

Guarantor

The corresponding author is the guarantor of submission.

Conflict of Interest

Authors declare no conflict of interest.

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