Case Report

Ofloxacin-ornidazole fixed-dose combination medication-induced pancreatitis with positive rechallenge

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Abstract

Although ofloxacin-ornidazole fixed-dose combination (FDC) is a rampantly used antibiotic combination for mixed-infection diarrhea in India, the adverse drug reaction (ADR) associated with these FDCs remains underreported. Herein, the authors present a case report of a definitive ofloxacin-ornidazole FDC-induced pancreatitis. The nonalcoholic adult male patient showed a sharp piercing epigastric pain flowing to the back, gradually rising in severity, which started after taking ofloxacin-ornidazole FDC tablet over the counter. Serum lipase concentration measured in the emergency room was 635 units per liter (normal range- 13–60 units/L) and serum amylase was 377 units/L (normal range- 30–110 units/L). Ultrasonography and an axial computed tomography of the abdomen confirmed the diagnosis of acute pancreatitis. Ofloxacin-ornidazole FDC tablet was stopped immediately. Past treatment records confirmed accidental rechallenge. In conclusion, this is a first case report of ofloxacin-ornidazole FDC-induced pancreatitis.

Keywords: Adverse event, ofloxacin, ornidazole, pancreatitis, positive rechallenge

Introduction

Drugs account for 1–5% of the total pancreatitis cases, sometimes the third most common after alcohol and gallstones.[1,2] Criteria to conclude the drug as an etiology for pancreatitis includes the following: requirement of temporal association establishment, ruling out the other causes of the disease, symptomatic betterment on dechallenge of the putative drug, and recurrence of symptoms on rechallenge.[3] The US FDA recently issued a warning of dysglycemia with certain fluoroquinolones such as ofloxacin, ciprofloxacin, gemifloxacin, levofloxacin, and moxifloxacin based upon post-marketing reviews in the USA.[4] These drugs penetrate the pancreatic tissues and help in the management of the infectious etiology; however, adverse events such as pancreatitis remain underreported to an extent that there are very few case reports of ciprofloxacin-induced pancreatitis.[5] On a similar note, metronidazole, a nitroimidazole, is known to be associated with the adverse event of pancreatitis. The extent of association between this nitroimidazole-induced pancreatitis rises to eight folds in the presence of other drugs like amoxicillin and proton pump inhibitors, commonly co-prescribed in management of *Helicobacter pylori*-induced peptic ulcer disease. The congener of same class ornidazole on its own has been infrequently linked to pancreatitis in the literature.[6] Herein, we present the case report where naturally occurring rechallenges at the patient's end established the ofloxacin-ornidazole fixed-dose combination-induced (FDC-induced) pancreatitis.

Case Report

A 36-year-old Asian Indian male came to the triage room of our hospital with recent-onset abdominal pain. The pain was largely centered in the upper middle quadrant, which was piercing type,

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7/10 on the severity scale, radiating to back, worsening with any move, and improving with respite. He disclaimed being suffering from any other illness except generalized anxiety disorder on the current illness history. His medical history was only substantial for hypovitaminosis D, for which he completed the vitamin D supplementation treatment course 1 month back. There was no positive surgical history. He was not consuming any drugs except amitriptyline for anxiety disorder for the past 8 years. The only medicine patient consumed preceding pain onset was ofloxacin-ornidazole FDC (200 mg ofloxacin and 500 mg ornidazole containing) tablet. The abdominal pain started 2 h after oral intake of ofloxacin-ornidazole FDC tablet obtained without prescription, reaching sufficient severity by 12 h requiring medical consultation in an emergency room. On further questioning, the patient recalled that 3 years ago he had similar abdominal pain that developed after taking ofloxacin-ornidazole FDC (with the different brand name) and had to see a doctor in an emergency. He was diagnosed as acute pancreatitis [Table 1]. The pain of the past episode responded within a few minutes to hours to painkiller injection with a reduction in the food intake on the clinician's advice. The patient is nonalcoholic; has never smoked or taken any recreational drugs. On evaluation, his vitals were stable. Tenderness was elicited in epigastrium on palpation without any guarding or the rigidity. Biochemical examination showed a raised concentration of lipase 635 units/L and amylase 377 units/L in the serum. CT examination of the abdomen was noteworthy for grade C acute pancreatitis (peripancreatic and perirenal fat stranding) with no collection formation [Figure 1]. Ultrasound examination of the abdomen ruled out the possibility of gallstone [Table 1]. The patient had normal triglycerides and calcium levels had no present or history of sepsis, injury, malignancy, or scorpion bite.

Discussion

The patient improved on dechallenge and natural rechallenge confirmed the association. On careful history, the patient had visited a local physician for suspected mixed infection diarrhea 3 years back. He was prescribed ofloxacin-ornidazole FDC which steered similar nature epigastric pain and was later concluded upon investigations to be an episode of acute pancreatitis. The severity of pancreatitis was mild and was managed with analgesic injection with conservative management.

Most of the times the acute diarrheas are self-limiting further questioning the use of FDCs Rampant prescriptions and over-the-counter sale of this specific "Indian" FDC gave birth to a pharmaceutical market share of more than 200 crore INR with more than 65 brands of ofloxacin-ornidazole FDC available in the Indian market.[7] Despite treatment guidelines suggesting against it, ofloxacin-ornidazole's combination use in Indian practice is increasing the frequency of ADRs, cost of treatment, and morbidity.[8] Drug-induced pancreatitis becomes even more relevant in the scenario of the Indian FDC drugs market where the quality of active drug comes under legal scanner. FDC is assumed to be a new drug and the Central Drugs Standard Control Organization (CDSCO), after meticulous examination of data on rationality, safety, and efficacy, generally issues approval as per section 122E of Drugs and Cosmetics Act 1940. Certain State Licensing Authority (SLA) of India gave manufacturing and marketing permission for the FDC producing firms without asking for no objection from CDSCO. The lack of communication between the CDSCO and SLAs led to legal case form after the government banned more than 300 irrational FDCs recently.[9]

The mechanism of an adverse event in the current patient scenario could be hypersensitive as the symptoms start within a few hours post drug intake. Similar ciprofloxacin-induced mild acute pancreatitis which starts shortly after drug intake was reported by Sung *et al.*[5] To our knowledge, this is the first case report of ofloxacin-ornidazole FDC-induced mild acute pancreatitis with positive rechallenge.

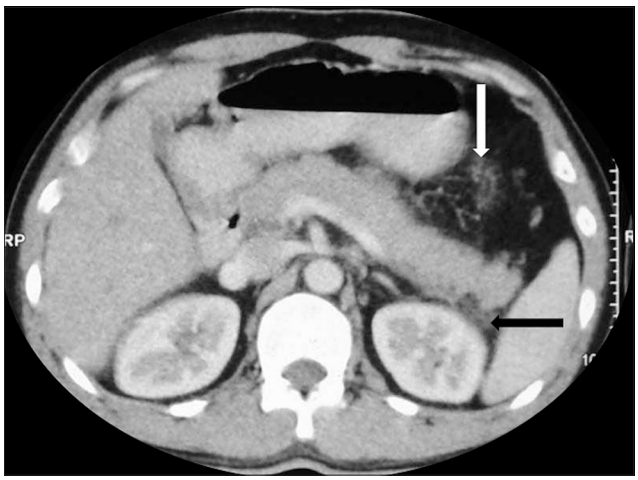

Figure 1: Abdominal CT image of current illness. Axial image from abdominal computed tomography showing the perirenal and peripancreatic fat stranding (black and white arrows, respectively) with no collection formation

Table 1: Temporality establishment with laboratory and radiological examination

Parameter	For current episode (Year 2019)	For prior episode (Year 2015)	Normal range
Amylase (U/L)	377	551	28-100
Lipase (U/L)	635	290	13-60
Endoscopic ultrasound	Multiple hyperechoic foci, strands, lobules in pancreatic body, tail and head, pancreatic duct not seen	--	NA
CT abdomen findings	Grade C pancreatitis with no collection formation	Mild bulky pancreas, slightly decreased enhancement, No calcification/duct dilatation, thickening of left Gerota's fascia (Grade C acute pancreatitis)	NA

Conclusion

This study emphasizes the need to remain watchful for the ofloxacin-ornidazole FDC, commonly used antibiotic in gastrointestinal or abdominal infections, due to its association with cases that are unusual, life-threatening, and require emergency care.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms in which the patient has given his consent for his images and other clinical information to be reported in the journal. The patient understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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