

Recurrent pancreatitis induced by metronidazole re-exposure and a review of the current literature

Mesut Yilmaz¹, Oguz Kinikoglu, Bahadir Ceylan, Ferhat Arslan², Ali Mert

(1) Istanbul Medipol University, Infectious Diseases & Clinical Microbiology. (2) Istanbul Medipol University, Infectious Diseases & Clinical Microbiology

To the Editor,

Metronidazole is the drug of choice used to treat parasitic infections, infections caused by anaerobic bacteria, *Helicobacter pylori*, inflammatory bowel diseases, and *Clostridium difficile* colitis. It is well distributed into body tissues and effectively penetrates the blood-brain barrier.

Acute pancreatitis is an inflammatory disease with a wide spectrum of severity, characterized by high levels of amylase and lipase (1). Severe epigastric pain of acute onset often radiating through the back is the main alarming symptom. Pancreatitis is a very rare adverse effect and only nine cases of metronidazole-induced pancreatitis have been reported in the English literature so far (Table 1) (2-10). We report a case of recurrent acute pancreatitis associated with oral metronidazole therapy for an episode of ulcerative colitis and *C. difficile* colitis.

A 22-year-old male was admitted to our hospital because of abdominal pain. Six months prior to his current admission, he was started ciprofloxacin and metronidazole as subsequent therapy for ulcerative colitis. Three days after initiation of antibiotics he was admitted to the emergency department with vomiting and gripping epigastric pain. He denied any alcohol use. Upon further investigations he was diagnosed with acute pancreatitis of undefined cause.

Prior to current admission, while he was being evaluated for another episode of bloody diarrhea, his stool tested positive for *C. difficile* antigen and toxin A and B. He was started metronidazole for treatment of *C. difficile* enterocolitis.

His gripping epigastric pain recurred. His serum amylase was elevated to 387 IU/L and serum lipase to 400 U/L. He was diagnosed with mild acute pancreatitis and improved in 3 days. However, his stool still tested positive for *C. difficile* antigen and toxin A and B. He was started metronidazole for the third time. He presented with the same abdominal symptoms. Serum amylase was 427 IU/L and lipase was 429 IU/L. There was no evidence of cholelithiasis or gallbladder stones on ultrasonography. An abdominal CT scan showed pancreatic swelling and peripancreatic infiltration, suggesting acute pancreatitis. A cause-and-effect relationship between metronidazole and repeated episodes of pancreatitis was highly suggestive of metronidazole-induced pancreatitis.

The patient was discontinued metronidazole. He was treated with oral vancomycin 125 mg q6h for *C. difficile* infection. His symptoms resolved and serum amylase returned to normal values within six days after conservative management and the patient was discharged without sequelae.

Drugs are relatively rare causes of acute pancreatitis with an estimated rate of 0.1-2% (11). Specific criteria described by Mallory et al. to support drug induced pancreatitis are; 1) pancreatitis that develops during treatment with the drug; 2) other likely causes of pancreatitis are not present; 3) pancreatitis that resolves upon discontinuing the drug; 4) pancreatitis that usually recurs upon readministration of the drug (8, 12).

In all but one of 21 episodes of pancreatitis reported in 10 cases (including our case) in the literature, pancreatitis developed in less than 8 days after initiation of metronidazole. Our patient developed acute pancreatitis on three different occasions and his presentation was within 72 hours of drug use in each episode. On neither occasion could any other etiology be identified, in particular gallstones were ruled out by imaging studies on all admissions. The probable etiology in his first episode was only evident when he presented with acute pancreatitis following metronidazole use for second and third times. Resolution of symptoms upon discontinuing metronidazole also supported our diagnosis about our case.

Metronidazole related acute pancreatitis is relatively rare. Physicians should keep this entity in mind especially when dealing with acute pancreatitis patients of undetermined cause. Discontinuation of the drug is essential for recovery and a rechallange should be avoided.

Correspondence to: Mesut Yilmaz, Istanbul Medipol University, Infectious Diseases & Clinical Microbiology. E-mail: myilmaz@medipol.edu.tr

Submission date: 02/04/2016

Acceptance date: 12/05/2016

Table 1. — Summary of case reports with metronidazole-induced pancreatitis in English literature

Reference, Author, Year	Age (years)	Gender	Episode	Time interval for Metronidazole to Pancreatitis (days)	Indications for Metronidazole
[2], Plotnick BH, 1985	29	Female	1 2	1 37	Postpartum unspecified vaginitis Unspecified vaginitis
[3], Sanford KA, 1988	63	Female	1	7	Crohn's disease
[4], Celifarco A, 1989	61	Female	1	4	Aspiration pneumonia
[5], Corey WA, 1991	49	Female	1 2	3-5 <1	Trichomoniasis Trichomoniasis
[6], Sura ME, 2000	23	Female	1 2, 3, 4	8 3-7	Bacterial vaginosis Bacterial vaginosis
[7], Feola DJ, 2002	22	Female	1 2, 3	<1 1	Unspecified vaginitis Unspecified vaginitis
[8], Nigwekar SU, 2004	46	Female	1 2	8 8	Bacterial vaginosis Bacterial vaginosis
[9], Loulergue P, 2008	25	Male	1	5	Pseudomembranous colitis
[10], O'Halloran E, 2010	25	Female	1 2	2 1	Endodontic abscess Endodontic abscess
Present case	22	Male	1 2, 3	3 2-3	Ulcerative colitis C. difficile colitis

References

1. TRIESTER S.L., KOWDLEY K.V. Prognostic factors in acute pancreatitis. *J. Clin. Gastroenterol.*, 2002, **34** : 167-76.
2. PLOTNICK B.H., COHEN I., TSANG T., CULLINANE T. Metronidazole-induced pancreatitis. *Ann. Intern. Med.*, 1985, **103** : 891-2.
3. SANFORD K.A., MAYLE J.E., DEAN H.A., GREENBAUM D.S. Metronidazole-associated pancreatitis. *Ann. Intern. Med.*, 1988, **109** : 756-7.
4. CELIFARCO A., WARSCHAUER C., BURAKOFF R. Metronidazole-induced pancreatitis. *Am. J. Gastroenterol.*, 1989, **84** : 958-60.
5. COREY W.A., DOEBBELING B.N., DEJONG K.J., BRITIGAN B.E. Metronidazole-induced acute pancreatitis. *Rev. Infect. Dis.*, 1991, **13** : 1213-5.
6. SUR A M.E., HEINRICH K.A., SUSENO M. Metronidazole-associated pancreatitis. *Ann. Pharmacother.*, 2000, **34** : 1152-5.
7. FEOLA D.J., THORNTON A.C. Metronidazole-induced pancreatitis in a patient with recurrent vaginal trichomoniasis. *Pharmacotherapy*, 2002, **22** : 1508-10.
8. NIGWEKAR S.U., CASEY K.J. Metronidazole-induced pancreatitis. A case report and review of literature. *JOP*, 2004, **5** : 516-9.
9. LOULERGUE P., MIR O. Metronidazole-induced pancreatitis during HIV infection. *AIDS*, 2008, **22** : 545-6.
10. O'HALLORAN E., HOGAN A., MEALY K. Metronidazole-induced pancreatitis. *HPB Surg.*, 2010, 523468.
11. BALANI A.R., GRENDLELL J.H. Drug-induced pancreatitis : incidence, management and prevention. *Drug Saf.*, 2008, **31** : 823-37.
12. MALLORY A., KERN F. Jr. Drug-induced pancreatitis : a critical review. *Gastroenterology*, 1980, **78** : 813-20.