Acute Pancreatitis Secondary to Ciprofloxacin Therapy in Patients with Infectious Colitis

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Background/Aims: Ciprofloxacin is considered to be a safe and effective treatment for acute infectious colitis. However, this drug may cause drug-induced pancreatitis, albeit rarely. **Methods:** From March 2007 to February 2012, we studied 227 patients who were hospitalized for infectious colitis at St. Mary's Hospital. All of the patients received ciprofloxacin therapy for the treatment of infectious colitis. We observed a few cases of rare adverse events, including ciprofloxacin-induced acute pancreatitis diagnosed based on the Naranjo algorithm. **Results:** During ciprofloxacin therapy, seven of 227 patients (3.1%) developed rare pancreatitis as defined by the Naranjo algorithm; pancreatic enzyme activity was sporadically elevated with ciprofloxacin use. After ciprofloxacin administration, the average interval until the development of pancreatitis was 5.5 days (range, 4 to 7 days). On abdominal computed tomography, pancreatic swelling and homogenous enhancement was noted in three of seven patients. Complicating acute pancreatitis was gradually but completely resolved after cessation of ciprofloxacin administration. The mean recovery time was 11.3 days (range, 8 to 15 days). **Conclusions:** We observed that ciprofloxacin-induced pancreatitis may occur with an incidence of approximately 3%. Ciprofloxacin-induced pancreatitis presents a short latency, suggesting an idiosyncratic hypersensitivity reaction. Practitioners should be aware that drug-induced pancreatitis can occur during ciprofloxacin therapy. **(Gut Liver 2014;8:265-270)**

Key Words: Anti-bacterial agents; Pancreatitis; Drug toxicity; Infectious colitis

INTRODUCTION

Ciprofloxacin, a synthetic 4-quinolone derivative, is a widely used, broad-spectrum antibiotic.[1] Generally, it is considered to be a safe and effective treatment of acute infectious colitis.[2,3] Additionally, it is a widely used empirical therapy for travelers' diarrhea.[4] However, ciprofloxacin can, in rare cases, cause drug-induced pancreatitis. Until now, there has only been one case report associated with ciprofloxacin in the literature.[5] In March 2007, we observed ciprofloxacin-induced pancreatitis in a patient with infectious colitis during therapeutic use. Since 2007, we have been aware that drug-induced pancreatitis can occur during ciprofloxacin therapy. And we have continued monitoring chemical profiles during ciprofloxacin use in patients with infectious colitis. As a result, here we describe seven patients who developed acute pancreatitis after receiving ciprofloxacin to treat infectious colitis. The patients with infectious colitis were kept nil per os (NPO; keeping off ingestion) other than ciprofloxacin during treatment of infection colitis, so other drug effects can be excluded completely. As a result, we think that hospitalized patients with infectious colitis are a good cohort to discriminate side effects of ciprofloxacin. The study's aim was to identify the clinical features and natural course of drug-induced pancreatitis by ciprofloxacin during therapeutic use.

MATERIALS AND METHODS

1. Patients

Between March 2007 and February 2012, 227 patients were hospitalized for moderate to severe infectious colitis at St. Mary's Hospital, Seoul, Korea. Infectious colitis was diagnosed according to clinical history with colonoscopy finding. After

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admission, they were enrolled in the infectious colitis registry. At initial admission, all patients received ciprofloxacin therapy while keeping NPO for bowel rest. During ciprofloxacin therapy, rare adverse events suggesting drug-induced pancreatitis were recorded in a few patients. In these cases, we stopped ciprofloxacin and recorded their clinical features while administering conservative treatment. We excluded the patients who had acute pancreatitis at initial admission or who had gallstones or common bile stones from this registry.

2. Clinical assessment and management in patients with infectious colitis

The patients visited our emergency department because of severe abdominal pain, diarrhea, and/or vomiting for several days. At initial admission, all patients were assessed via colonoscopy and blood chemical profiles such as hemoglobin, white blood cell, aspartate aminotransferase, alanine aminotransferase, γ-glutamyl transpeptidase (γ-GTP), amylase, and lipase. Initially, abdominal computed tomography was performed to exclude vascular insufficiency or other diseases. After admission, patients were started on intravenous ciprofloxacin therapy (400 mg of intravenous ciprofloxacin two times daily for 3 days to 4 days). They were kept NPO for a bowel rest with parenteral nutritional support. If their abdominal pain and diarrhea were improved, they receive a soft diet and oral ciprofloxacin therapy (500 mg of oral ciprofloxacin two times daily for 3 days to 5 days). Chemical profiles were monitored regularly, once every 3 days. If an adverse event was recorded on chemical profiles during ciprofloxacin therapy, the therapy was ceased, and clinical feature were observed while conservative treatment was administered. All patients were monitored using the Naranjo algorithm for assessing probability of an adverse drug reaction.[6]

3. Statistical analysis

We assessed whether initial demographic variables were associated with drug-induced pancreatitis by ciprofloxacin. All statistical analyses were performed using the SPSS version 12.0 (SPSS Inc., Chicago, IL, USA). Pearson chi-square test was used for comparison of the categorical variables. Statistical comparisons of the symptom score between the normal and abnormal test group was performed using an independent-samples t-test. For all tests, the significance level was established at a value of p<0.05.

4. Ethical considerations

This study was approved by the Institutional Review Board (IRB) at the St. Mary's Hospital of The Catholic University of Korea College of Medicine (IRB number, SC11RISI0065). The study was carried out in accordance with the recommendations of the Declaration of Helsinki.

RESULTS

1. Demographic characteristics

Between March 2007 and February 2012, 227 patients were hospitalized and enrolled in an infectious colitis registry at St. Mary's Hospital (113 males and 114 females with a mean age of 50.5±21.8 years; range, 14 to 92 years). Mean hospital stay was 5.1±5.3 days. After admission, all patients received intravenous ciprofloxacin and nutritional support. Ciprofloxacin was a safe and effective drug for the treatment of infectious colitis in 220 of 227 (96.9%) patients. These patients successfully recovered from infectious colitis. However, seven of 227 patients (3.1%) experienced an adverse event (four males and three females with a mean age of 46.9±17.4 years; range, 24 to 71 years). Clinical characteristics are summarized at Table 1. The development of drug-induced pancreatitis had no relation with age or sex (p=0.33, p=0.36, respectively). The total duration of hospital stay was much longer in patients with drug-induced pancreatitis (5.1±5.3 vs 19.0±6.8, p=0.002).

2. Diagnosis of drug-induced pancreatitis

Seven patients showed abnormal pancreatic enzymes; amylase and lipase levels were elevated. Pancreatitis was diagnosed by the concurrence of at least two of the following findings:[7] 1) newly onset epigastric abdominal pain during admission; 2) elevated serum amylase and lipase levels at three times the upper level of the normal range; and 3) imaging evidence of pancreatic inflammation on radiologic study. In all seven cases described, other causes of pancreatitis were completely ruled out. None of the patients had significant alcohol use, nor were there family histories of pancreatitis. Cholelithiasis was not present, and triglyceride levels were normal. Furthermore, all the seven patients were not receiving any medications except for ciprofloxacin. They were kept NPO after admission with infectious colitis for bowel rest. Having probable pancreatitis was considered secondary to ciprofloxacin by the Naranjo algorithm.[6] After ciprofloxacin administration, the average time interval until development of pancreatitis was 5.5 days (range, 4 to 7 days) (Table 1, Fig. 1). This short time frame of latency suggests a hypersensitivity reaction. Abdominal imaging was performed to exclude other possible causes of pancreatitis and to assess the severity of pancreatitis. Abdominal imaging did not show gallstones or gallbladder wall thickening in any of these patients. Pancreas swelling and homogenous enhancement were noted in three of seven patients (42.9%) (Figs 2 and 3).

3. Treatment option for drug-induced pancreatitis and therapeutic efficiency after conservative care

In cases of adverse reactions, we immediately stopped ciprofloxacin administration. These patients were kept NPO with parenteral nutritional support. The treatment was targeted to pancreatic enzyme intravenous Gabexate Mesilate (Foy inj®,

Table 1. Demography and Clinical Characteristics of Drug-Induced Pancreatitis Secondary to Ciprofloxacin Use

Case no.	Age	Sex	Severity/ Extent of colitis	Dose/Duration of ciprofloxacin	Initial amylase*/Lipase[†]	Peak amylase/Lipase	Pancreas imaging	Pancreatitis developing time, day	Recovery time, day
1 D.W.J.	34	M	Severe/ pancolitis	800 mg IV for 2 days/ 1,000 mg PO for 5 days	55/49	347/1,204	Mild swelling	6	14
2 K.Y.K.	71	M	Severe/ sigmoid–rectum	800 mg IV for 2 days/ 1,000 mg PO for 3 days	103/51	667/1,566	Swelling/homogenous enhancement	6	20
3 S.I.L.	58	F	Severe/ pancolitis	800 mg IV for 2 days/ 1,000 mg PO for 4 days	50/54	243/418	Nonspecific finding	8	8
4 H.S.H.	24	F	Moderate/ cecum–ascending	800 mg IV for 5 days	101/48	520/1,963	Mild swelling	6	23
5 J.S.Y.	51	F	Severe/ cecum–ascending	800 mg IV for 5 days	49/19	227/427	Nonspecific finding	6	14
6 S.H.L.	31	M	Moderate/ cecum–ascending	800 mg IV for 4 days	92/15	221/144	Nonspecific finding	5	7
7 G.W.P.	59	M	Moderate/ cecum–ascending	800 mg IV for 2 days	115/102	677/1,405	Swelling/peripancreatic inflammation	3	6

M, male; F, female; IV, intravenous; PO, per oral.
*Normal range of amylase, 45 to 160 IU/L; [†]Normal range of lipase, 13 to 60 U/L.
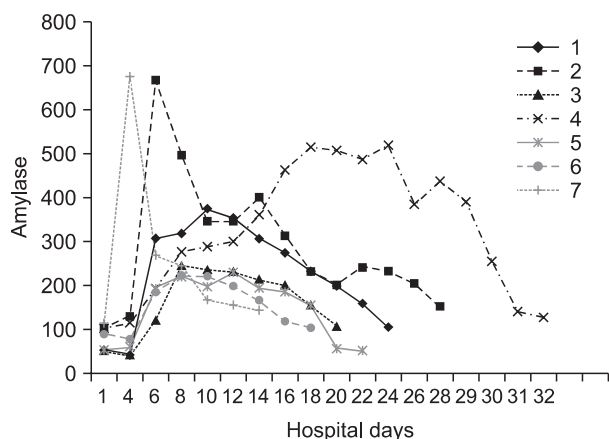

Fig. 1. Laboratory findings of drug-induced pancreatitis by ciprofloxacin. Among 227 patients who received ciprofloxacin, seven (3.1%) demonstrated an adverse reaction; the pancreatic enzyme levels spiked after ciprofloxacin injection. Ciprofloxacin has a latency of 4 to 7 days from the beginning of drug infusion to the development of acute pancreatitis. This short time frame suggests a hypersensitivity reaction.

200 mg/day; Dong-A ST Co., Seoul, Korea) was given for several days for acute pancreatitis. If the pancreatic enzyme was declined, treatment was changed to per oral Camostat Mesilate (Foipan®, 300 mg/day; Ilsung Co., Seoul, Korea) until the chemical profile returned to normal. Complicating acute pancreatitis was completely resolved gradually after the removal of ciprofloxacin. Mean recovery time for drug-induced pancreatitis was 11.3 days (range, 8 to 15 days) (Table 1, Fig. 1). The patients had no further abdominal pain episodes and remained stable for the remainder of the hospital day. All the patients have been doing well and denied any gastrointestinal symptoms. After discharge,

an outpatient follow-up of blood chemistries demonstrated that the pancreatic enzyme stayed in the normal range.

DISCUSSION

Ciprofloxacin is now widely used for a number of conditions and, in particular, is thought to be appropriate for early self-treatment of moderate to severe travelers' diarrhea in adults.[4] Additionally, it is considered to be a safe and effective treatment for acute infectious colitis.[2,3] Its lack of serious adverse effects has been an important factor in its use for what is usually a benign, self-limiting condition. Of 63,059 patients given oral ciprofloxacin, adverse effects occurred in 5.8% of patients, with 3.4% being of a gastrointestinal nature.[7] The U.K. Medicine Control Agency received 635 reports of serious reactions per 1 million prescriptions of ciprofloxacin since the drug launch in 1987 through 1995.[7] Common gastrointestinal side effects include diarrhea, *Clostridium difficile* enterocolitis, and abnormalities of liver biochemistry. The drug is generally associated with mild, reversible elevation of liver enzymes and bilirubin in approximately 2% to 3% of patients.[2] In the pancreatic field, ciprofloxacin can be a useful tool as an empirical therapy in necrotizing pancreatitis to prevent secondary bacterial infection,[8-11] because ciprofloxacin penetrates the human pancreas very well.[12,13] However, ironically, it is claimed that the ciprofloxacin can, in rare cases, cause drug-induced pancreatitis. Until now, there has only been one case report associated with ciprofloxacin in the literature.[5] Since March 2007, we observed seven cases of ciprofloxacin-induced pancreatitis in patients with infectious colitis during therapeutic use. In the prior report, the first episode of pain was undiagnosed, the clinical features
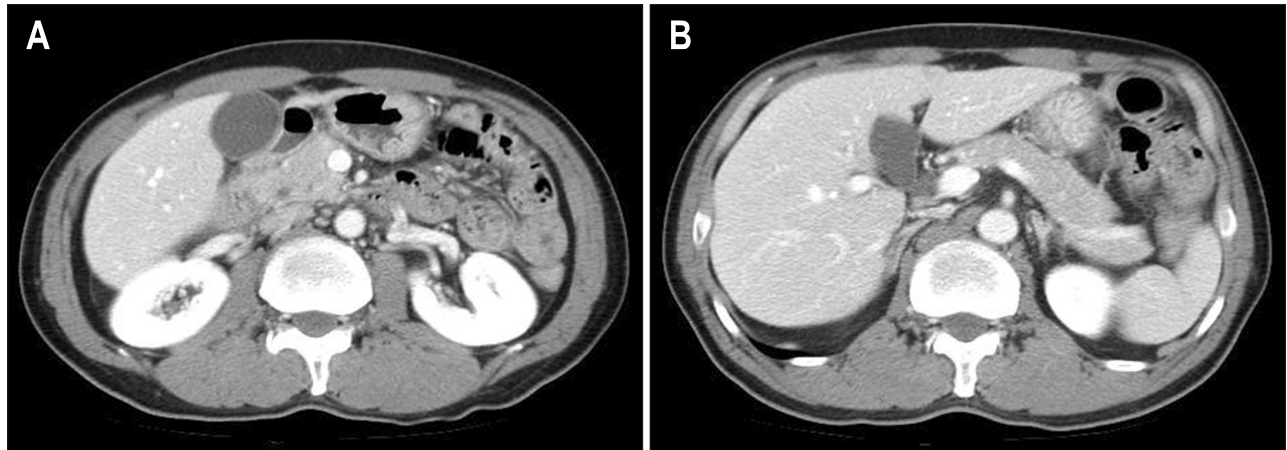
Fig. 2. A 58-year-old Korean male presented to the emergency department of our institution with a 4-day history of lower abdominal pain with diarrhea and fever. He was diagnosed with infectious colitis. The results of an initial chemical profile were within the normal ranges. He received 400 mg of intravenous ciprofloxacin twice daily for 2 days while remaining nil per os for bowel rest. On the third day of treatment, he complained of severe abdominal pain. At this time, his serum amylase and lipase activities were elevated to 677 U/L (reference range, 45 to 160 IU/L) and 1,405 U/L (reference range, 42 to 168 mg/dL), respectively. (A, B) Abdominal computed tomography demonstrated swelling of the pancreatic head and peripancreatic inflammation. (A) Mild swelling of the duodenal second and third loops was noted. The patient was diagnosed with probable drug-induced pancreatitis secondary to ciprofloxacin using the Naranjo algorithm for assessing the probability of an adverse drug reaction.[11]
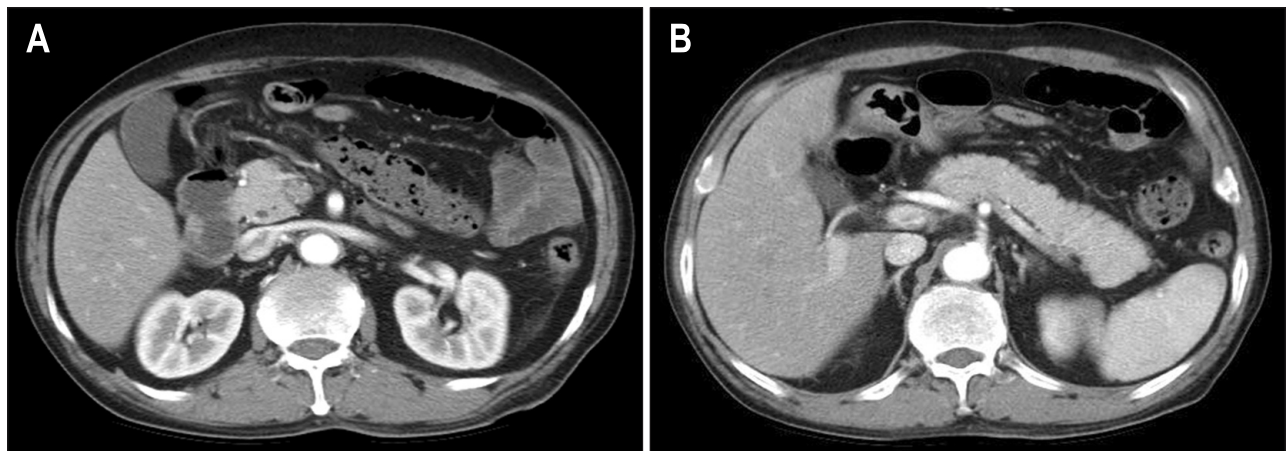

Fig. 3. A 71-year-old male presented to the emergency department of our institution with nausea, vomiting, and watery diarrhea over the previous 3 days. Amylase and lipase levels were normal at 130 U/L (reference range, 45 to 160 IU/L) and 51 U/L (reference range, 13 to 60 U/L), respectively. The patient was given 400 mg of intravenous ciprofloxacin twice daily for 2 days. Subsequently, he was given 500 mg of oral ciprofloxacin twice daily for 3 days. On the sixth day of treatment, follow-up laboratory parameters worsened; the serum amylase and lipase activities were elevated to 246 and 566 U/L, respectively. (A, B) Seven days after admission, abdominal computed tomography demonstrated swelling and homogeneous enhancement of the pancreas head and body. The patient was managed conservatively and had an uneventful recovery, and has remained well since discharge. He was diagnosed with probable drug-induced pancreatitis secondary to ciprofloxacin based on the Naranjo algorithm.[11]

were compatible with acute pancreatitis and on rechallenge with the same drug 18 months later, a similar episode of pain was confirmed as acute pancreatitis.[5] Drug-induced pancreatitis is a rare cause of acute pancreatitis, accounting for approximately 2% to 5% of all cases of pancreatitis.[2-4,14] In our hospital, total number of acute pancreatitis patients during the study was 251. Out of 251 acute pancreatitis patients reported during the study, 11 cases were found to be drug-induced, accounting for 4.4% (11/251). Possible drugs that may have caused the acute pancreatitis include ciprofloxacin which is suspected to be responsible for seven cases, augmentin for one, anticancer drug tacrolimus for one, anti-inflammatory caridase for one, diuretics for one. However, these speculations were not rechallenged by retrospective studies, and thus not confirmed.

Drug-induced pancreatitis is not a negligible disease, but it is hard to diagnose. The most frequently implicated medications are metronidazole, tetracycline, azathioprine, furosemide, thiazide diuretics, angiotensin converting enzyme inhibitors, didanosine, aspirin, valproic acid, and codeine.[1,15,16] The pathogenetic mechanism of drug-induced pancreatic injury remains unclear.

The pathophysiology is likely an idiosyncratic hypersensitivity reaction that differs among the aforementioned medications depending on their chemical structures. A positive rechallenge is considered when the drug is stopped after a patient is found to have acute pancreatitis and after resolution of the pancreatitis, when the drug is restarted, acute pancreatitis develops again. However, due to the character of the disease and ethical considerations, rechallenge is usually unintended. Despite the lack of a rechallenge, a drug may also be strongly suspected if there is a consistent latency among the case reports between initiating the drug and the onset of acute pancreatitis. A consistent latency may be a sign that the drug has a common mechanism of action.[17] In our cases, ciprofloxacin had a latency from drug administration to the development of acute pancreatitis of 4 to 7 days. This short time frame suggests a hypersensitivity reaction.[17] In our observations, drug-induced pancreatitis caused by ciprofloxacin occurs at a low incidence of less than 3%. In most cases, the patient was not aware of typical symptoms of acute pancreatitis. The prognosis of drug-induced pancreatitis by ciprofloxacin is good. We had the patients fast and quit the drug suspected of inducing acute pancreatitis meanwhile continuously intravenous administrating gabexate mesilate. Elevated enzyme levels of amylase and lipase improved dramatically within a week after stopping drug administration. Ciprofloxacin is a broad spectrum antibiotic and is widely used to treat a number of conditions. However, the question of why ciprofloxacin-inducing pancreatitis is rarely observed remains. The answer to this is quite simple: routine screening of the chemical profile has been overlooked, despite the risk of an adverse event. It is important that practitioners be aware that this potential adverse effect may be occurring. We advise more caution in recommending this antibiotic for therapeutic use or empirical use. Close monitoring for an adverse event may be necessary. During ciprofloxacin use, regular screening of chemical profiles including amylase, lipase, liver enzyme, and creatinine is warranted. We consider it necessary that larger, prospective studies aimed at drug-induced pancreatitis caused by ciprofloxacin be conducted.

We described seven cases of ciprofloxacin-induced acute pancreatitis; the patients' pancreatic enzymes were at a normal range at initial admission. Pancreatic enzyme was sporadically elevated with ciprofloxacin use. We observed that ciprofloxacin-induced pancreatitis may occur with an incidence of approximately 3%. Drug-induced pancreatitis by ciprofloxacin displays a short latency, suggesting an idiosyncratic hypersensitivity reaction. If pancreatitis was detected early, the prognosis was very good, and all of our patients fully recovered within 3 weeks. Although the exact mechanism for this reaction remains a mystery, ciprofloxacin use may be considered a rare risk factor for the development of acute pancreatitis.

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