Internal Medicine
The Japanese Society of Internal Medicine
doi: 10.2169/internalmedicine.9681-22
Intern Med 62: 233-235, 2023
http://internmed.jp

【 CASE REPORT 】

Small Intestinal Perforation Caused by Enteric-coated Low-dose Aspirin

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Abstract:
A 77-year-old man presented with abdominal pain for 1 week. He was taking enteric-coated low-dose aspirin (LDA) to prevent secondary cardiovascular events and a proton pump inhibitor (PPI). Computed tomography indicated a small intestinal perforation; thus, small intestine resection was performed. Two months after surgery, he experienced a recurrence of the perforation. Since his repeated perforation was suspected to be due to LDA, LDA was discontinued. He has experienced no further recurrence since then. This is the first case of small intestinal perforation caused by enteric-coated LDA. Enteric-coated LDA may cause small intestinal perforation in patients with severe atherosclerosis under PPI administration.

Key words: aspirin, atherosclerosis, small intestinal perforation, proton pump inhibitor, case report

(Intern Med 62: 233-235, 2023)
(DOI: 10.2169/internalmedicine.9681-22)

Introduction

Low-dose aspirin (LDA) is widely used in clinical practice for primary and secondary prevention of cardiovascular and thrombotic cerebrovascular events (1-3). It is well known that LDA commonly causes upper gastrointestinal complications, such as peptic ulceration and bleeding.

To avoid gastric mucosal injury caused by LDA, two types of formulations (buffered aspirin and enteric-coated aspirin) have been designed. Buffered LDA suppresses gastric mucosal damage by increasing the solubility of aspirin, while enteric-coated LDA suppresses it by passing through the stomach without dissolution. Although enteric-coated aspirin use is reportedly associated with a lower frequency of gastroduodenal injuries than regular aspirin (4), one study showed that small intestinal damage was more frequent in patients taking enteric-coated aspirin than in those taking buffered LDA (5). In addition, proton pump inhibitor (PPI) administration increases the risk of small intestinal injury caused by LDA (6). Small intestinal damage caused by LDA is typically mild (5, 7). Although one case report indicated small intestinal perforation caused by indomethacin (8), small intestinal perforation caused by LDA has never been reported.

We herein report a case of a small intestinal perforation caused by enteric-coated LDA in a patient taking PPIs with multiple atherosclerotic risk factors.

Case Report

A 77-year-old man presented to our outpatient clinic with abdominal pain for the past week. The abdominal pain was intermittent at first but gradually became persistent. He had a history of percutaneous coronary intervention and pacemaker implantation and had been treated for type 2 diabetes, hypertension, dyslipidemia, hypothyroidism, prostatic hyperplasia, constipation, and hyperuricemia. The prescription drugs he was taking at the presentation are shown in Table.

A physical examination revealed a blood pressure of 127/65 mmHg; pulse rate, 73/min; body temperature, 37.3°C; and clearly conscious. He had lower abdominal tenderness. His laboratory test results were follows: white blood cell (WBC) count, 8,600/μL (neutrophil, 75%); blood urea nitrogen (BUN), 27.1 mg/dL; creatinine (Cr), 1.27 mg/dL; and C-reactive protein (CRP), 9.04 mg/dL, and the international normalized ratio of prothorombin time (PT-INR), 1.77.

Enhanced abdominal computed tomography (CT) revealed

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Received: March 2, 2022; Accepted: May 5, 2022; Advance Publication by J-STAGE: June 21, 2022
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Table. Prescription Drugs at the First Episode.

Enteric-coated aspirin	100 mg
Lansoprazole	15 mg
Warfarin potassium	3.5 mg
Verapamil hydrochloride	120 mg
Carvedilol	10 mg
Glimepiride	1 mg
Sitagliptin phosphate hydrate	50 mg
Imidapril hydrochloride	5 mg
Rosuvastatin calcium	5 mg
Levothyroxine sodium hydrate	25 μg
Naftopidil	25 mg
Magnesium oxide	500 mg
Febuxostat	20 mg

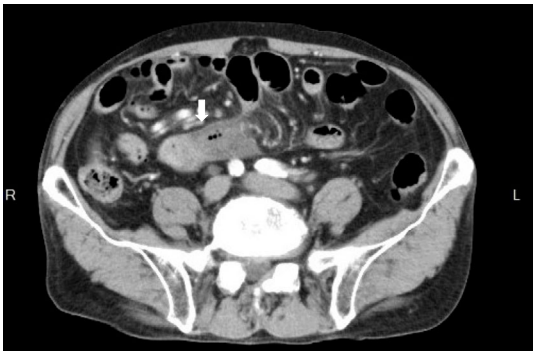

Figure 2. Enhanced abdominal CT show slight intraperitoneal air and rim-enhancing hypodensity collection (arrow).

discontinuity and focal thickening of the intestinal wall with adjacent extraluminal gas bubbles and localized increased mesenteric fat attenuation, indicating a small intestinal perforation with abscess (Fig. 1).

Emergency small intestinal resection was performed. The macroscopic finding of the resection specimen revealed two perforations of approximately 2 mm in the small intestine wall with a mesenteric abscess. No foreign body was found in the abscess. No ulcers or erosions were found aside from the two perforation sites. The microscopic examination of the resected intestine showed edema spreading from the submucosa to the muscle layer in the small intestine wall near the perforations, which suggested that the perforation had developed due to ischemia. His symptoms improved, and he was discharged nine days after surgery. His medications for comorbidities were continued.

Two months after the surgery, the patient presented to our outpatient clinic with recurrent abdominal pain. His abdomen was flat and soft, with mild tenderness in the lower abdomen. His laboratory test findings were as follows: WBC count, 4,600/μL (neutrophils, 68.6%); BUN, 26.8 mg/dL; Cr, 1.45 mg/dL; and CRP, 4.29 mg/dL. Enhanced abdominal CT revealed slightly intraperitoneal air and rim-enhancing hypodensity collection. We diagnosed recurrence of small intestinal perforation (Fig. 2). Because his abdominal pain

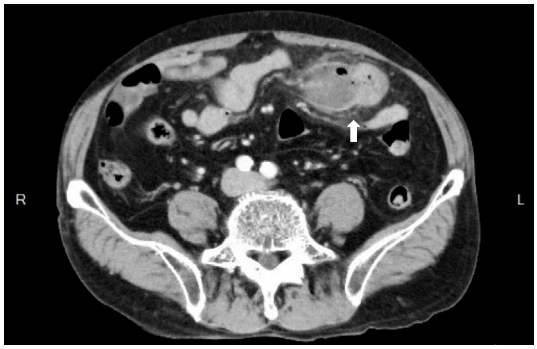

Figure 1. Abdominal contrast-enhanced computed tomography images show the bowel wall's discontinuity and focal thickening with adjacent extraluminal gas bubbles and localized increased mesenteric fat attenuation (arrow).

and abnormal CT findings were mild, we decided that he did not require surgery; thus, oral food intake was stopped, and antimicrobial agents were administered conservatively. His symptoms quickly improved after the conservative treatment, and he was discharged 12 days after the recurrent perforation.

As enteric-coated LDA intake was suspected as the cause of his repeated small intestinal perforation, administration of LDA was discontinued. Since the discontinuation of LDA administration, he has not experienced any recurrence of small intestinal perforation in the 16 months since the second episode.

Discussion

Based on our search of Pubmed on Octorber 12, 2021 using search strategy described below, this is the first case of a patient with small intestinal perforation caused by enteric-coated LDA.

#1 Add search ["Gastrointestinal Diseases"(mh) OR "intestinal perforation#(mh) OR (small bowel ulcer) OR (small bowel injury) OR (small bowel perforation) OR (small intestinal ulcer) OR (small intestinal perforation)]

#2 Add search ["Aspirin"(mh)]

#3 Add search #1 AND #2

#4 (small intestinal perforation)

#5 Add search [(perforation) AND "Intestine, Small"(mh) OR (small bowel ulcer)]

#6 Add search [(cause) AND #5]

#7 Add search [("Anti-Inflammatory Agents, Non-Steroidal"(mh) AND #5]

#8 Add search ["risk factors"(mh) AND (small bowel injury)]

#9 Add search (small bowel perforation)

#10 Add search ["Drug-Related Side Effects and Adverse Reactions"(mh) OR "risk"(mh)]

#11 Add search #9 AND #10

#12 Add search #3 OR #4 OR #6 OR #7 OR #8 OR #11.

At the first episode of the small intestinal perforation, we had no reason to suspect that enteric-coated LDA was the

cause. During the second episode of small intestinal perforation, however, we suspected LDA as the culprit, and after the discontinuation of LDA, the patient experienced no recurrence.

Enteric-coated LDA may increase the risk of small intestinal injury compared with buffered LDA. Nonsteroidal anti-inflammatory drugs (NSAIDs), including aspirin, commonly cause gastrointestinal disorders, which occur in up to 50% of patients with NSAIDs (9). Given that aspirin additionally causes dyspeptic symptoms in approximately 15-20% of patients (10, 11), enteric-coated LDA was developed to reduce gastric and duodenal damage. Gastroduodenal injury due to enteric-coated LDA is reportedly less frequent than that due to the buffered form (4). However, in recent years, some reports have indicated that enteric-coated LDA is more likely to cause small bowel injury than buffered LDA because of absorption in the small intestine (5, 6, 12).

A possible reason for the high proportion of small bowel injury in patients taking enteric-coated aspirin may be the prolonged retention of aspirin in the small bowel. The small bowel mucosa may be exposed to aspirin for a prolonged period, thereby promoting direct topical damage. Gastrointestinal disorders due to NSAIDs have been described as a "three-hit hypothesis." According to this theory, NSAIDs cause an increase in permeability of the gastroduodenal mucosa and small intestine mucosa. Through the increased intestinal permeability, various materials, such as bile acids, food, intestinal bacteria, and proteolytic enzymes, damage the weakened intestinal barrier, and secondary inflammation occurs by the activation of neutrophils (13). The changes in the intestinal microbiota caused by PPI administration increase the risk of small intestine lesions caused by LDA (6). Old age and hypertension are risk factors for the recurrence of small intestine injury due to NSAIDs (14). The recurrence of the symptoms in the present case was affected by these risk factors.

NSAIDs sometimes cause gastrointestinal perforation (15), but small intestinal perforation is rare, and only one case of small intestinal perforation caused by indomethacin has been reported (8). Furthermore, in patients with LDA-induced small intestinal injury, erosions and ulcers are common (5, 7), and gastrointestinal perforation has not been reported. Ischemia was indicated in the microscopic findings of the present case, and ischemia is a cause of non-traumatic gastrointestinal perforation (16). Atherosclerosis contributes to mesenteric ischemia (17). The present patient had a history of several atherosclerotic diseases. Thus, atherosclerosis may have led to small intestinal perforation in the present case.

In conclusion, we encountered a patient with small intestinal perforation caused by enteric-coated LDA. Enteric-coated LDA might cause small intestinal perforation in patients with severe atherosclerosis under PPI treatment. We should consider switching from enteric-coated LDA to buffed LDA or discontinuing PPIs altogether in patients with severe atherosclerotic diseases.

The authors state that they have no Conflict of Interest (COI).

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