Small-bowel mucosal injuries in low-dose aspirin users with obscure gastrointestinal bleeding

Junichi Iwamoto, Yuji Mizokami, Yoshifumi Saito, Koichi Shimokobe, Akira Honda, Tadashi Ikegami, Yasushi Matsuzaki

Iwamoto J and Shimokobe K analyzed the clinical data; Mizokami Y, Saito Y, Honda A, Ikegami T and Matsuzaki Y were also involved in editing the manuscript; Iwamoto J designed the study and wrote the manuscript.

Correspondence to: Junichi Iwamoto, MD, PhD, Department of Gastroenterology, Tokyo Medical University Ibaraki Medical Center, 3-20-1 Ami-machi Chuo, Inashiki-gun, Ibaraki 300-0395, Japan. junnki@dg.mbn.or.jp
Telephone: +81-29-8871161 Fax: +81-29-8883463
Received: December 10, 2013 Revised: January 18, 2014 Accepted: June 20, 2014 Published online: September 28, 2014

Abstract

AIM: To investigate the clinical differences between small intestinal injuries in low-dose aspirin (LDA) users and in non-steroidal anti-inflammatory drug (NSAID) users who were examined by capsule endoscopy (CE) for obscure gastrointestinal bleeding (OGIB).

METHODS: A total of 181 patients who underwent CE for OGIB were included in this study. Based on clinical records, laboratory data such as hemoglobin levels, major symptoms, underlying diseases, the types and duration of LDA and NSAID use, and endoscopic characteristics of CE were reviewed.

RESULTS: Out of a total of 45 cases of erosive lesions, 27 cases were taking LDA or NSAIDs (7 were on NSAIDs, 9 were on LDA alone, 9 were on LDA and thienopyridine, and 2 were on LDA and warfarin). The prevalence of ulcers or erosion during chronic use of LDA, LDA and the anti-platelet drug thienopyridine (clopidogrel or ticlopidine), and NSAIDs were 64.3%, 80.0%, and 75.0%, respectively. Erosive lesions were observed predominantly in chronic LDA users, while ulcerative lesions were detected mainly in NSAID users. However, concomitant use of thienopyridine such as clopidogrel with LDA increased the proportion of ulcers. The erosive lesions were located in the whole of the small intestine (jejunum and ileum), whereas ulcerative lesions were mainly observed in the ileum \((P < 0.05)\).

CONCLUSION: Our CE findings indicate that chronic LDA users and NSAID users show different types and locations of small-bowel mucosal injuries. The concomitant use of anti-platelet drugs with LDA tends to exacerbate the injuries from LDA-type to NSAID-type injuries.

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Key words: Non-steroidal anti-inflammatory drugs; Low-dose aspirin; Small-bowel mucosal injuries; Obscure gastrointestinal bleeding; Capsule endoscopy

Core tip: The aim of this study is to clarify the clinical feature of ulcerative or erosive lesion of small intestine in the long-term non-steroidal anti-inflammatory drug (NSAID) users who were examined by capsule endoscopy for obscure gastrointestinal bleeding. The ulcerative lesions were predominantly located in both jejunum and ileum or just in ileum while erosive lesions were predominantly found in both jejunum and ileum or just in jejunum significantly. These findings indicate the possibility that distribution of NSAID-induced small intestinal lesion differ according to the types of mucosal injury.
INTRODUCTION

It has been demonstrated that low-dose aspirin (LDA) and non-steroidal anti-inflammatory drugs (NSAIDs) increase the risk of gastroduodenal mucosal injury[1,2]. Recent reports using new methods of investigating the small intestine, such as double balloon endoscopy (DBE)[3] and capsule endoscopy (CE)[4], have also shown that NSAIDs can cause mucosal damage in the small intestine[5-8]. Obscure gastrointestinal bleeding (OGIB) is defined as bleeding of unknown origin that persists or recurs after a negative initial or primary upper endoscopy and colonoscopy and radiologic evaluation of the small bowel[9,10]. The clinical features of the ulcerative or erosive lesions of the small intestine in long-term NSAID users who were examined subsequently by CE for OGIB have not been sufficiently reported.

In the present study, 181 OGIB cases were examined with CE and were investigated with the following aims: to evaluate the prevalence of ulcerative or erosive lesions in the small intestine in chronic LDA or NSAID users in OGIB cases, to analyze the clinical features including endoscopic findings of these lesions, and to analyze the clinical course of these cases.

MATERIALS AND METHODS

Patients

Between June 2007 and September 2013, 181 patients who underwent CE for OGIB at Tokyo Medical University Ibaraki Medical Center were analyzed in this study.

CE

CE was performed using a PillCam SB (Given Imaging). Patients fasted for 10 h before capsule ingestion. Drinking clear fluids was allowed 2 h and eating a light snack was allowed 4 h after ingestion of the capsule. The data recorder was removed 8 h later, and the patients were subsequently discharged. Data were downloaded and interpreted by experienced endoscopists. The patients were asked to report any adverse events and to confirm excretion of the capsule in their stool.

Data analysis

Based on clinical records, laboratory data such as hemoglobin levels, major symptoms, underlying diseases, the types and duration of NSAIDs, and endoscopic characteristics of CE were reviewed. The morphologies of the lesions were classified into red spots, small erosion, large erosion, or ulcers as previously reported[7]. A red spot was defined as a red spot or crimson area of mucosa with presentation of villous architecture. A small erosion was defined as a circumscribed area of mucosal disruption denuded of villi with or without exudates or red color with a diameter equivalent to a valvulae conniventes. Large erosions were defined as circumscribed breaks in the mucosa larger than the equivalent diameter of a valvulae conniventes. In the present study, red spots, small erosion, and large erosion were included in the CE erosion results (Figure 1A). Ulcers were defined as large erosion with a central area with exudates[7] (Figure 1B).

The small bowel was divided into two segments (proximal and distal) equally on the basis of each subject’s small bowel transit time.

Statistical analysis

The continuous variables were expressed as mean values ± SD. We compared the categorical variables using the Fisher’s exact test and the continuous variables using the Mann-Whitney test. A P value of less than 0.05 was considered statistically significant.

RESULTS

Out of a total of 181 CE cases for OGIB, 13 cases (7.2%) were diagnosed as ulcerative lesions and 45 cases (24.9%) as erosive lesions of the small intestine. Out of a total of 13 cases of ulcerative lesions, 8 cases were taking LDA or NSAIDs (5 were on NSAIDs while 3 were on LDA and the anti-platelet drug, thienopyridine; clopidogrel). Out of a total of 45 cases of erosive lesions, 27 cases...
were taking LDA or NSAIDs (7 were on NSAIDs, 9 were on LDA alone, 9 were on LDA and thienopyridine, and 2 were on LDA and warfarin). Erosive lesions were observed predominantly in chronic LDA users, whereas ulcerative lesions were detected mainly in NSAID users (Figure 2).

The prevalence of ulcers or erosion during chronic use of LDA, LDA and thienopyridine, and NSAIDs was 64.3%, 80.0%, and 75.0%, respectively (Figure 3). The concomitant use of thienopyridine (clopidogrel) with LDA increased the proportion of ulcers from 0% to 20%.

The locations of erosive and ulcerative lesions are shown in Figure 4. The erosive lesions were located in the entire small intestine (jejunum and ileum), whereas ulcerative lesions were observed mainly in the ileum ($P < 0.05$).

Details of the characteristics of ulcerative lesions of chronic LDA or NSAID users are summarized in Table 1. In 4 of the 8 ulceration cases, LDA or NSAID was withdrawn. In 4 patients who had continued the LDA

DISCUSSION

The damage to the gastric and duodenal mucosa caused by NSAIDs is well established, and there has been increasing recognition of the damage caused to the mucosa of the small intestine by NSAID treatment. The pathogenesis of NSAID-induced small intestinal damage has been investigated, and a number of mechanisms may be implicated, including the toll-like receptor 4/MyD88-dependent pathway, dual inhibition of COX enzymes, enterohepatic circulation of NSAIDs, mitochondrial damage, and ischemia-reperfusion injury.

The prevalence of NSAID-induced small bowel lesions in the cases who had undergone CE or BDE for OGIB has also been investigated. A previous report has shown that among the 108 cases that underwent DBE for OGIB, 5 cases (4.6%) were diagnosed with NSAID-associated ulcers of the small intestine (3). A multicenter study has shown that 31 cases (4.7%) were diagnosed with NSAID-induced ulcerative lesions among 661 cases who underwent DBE for OGIB (6). In our present study, 4.4% and 14.9% of the cases were diagnosed with ulcerative lesions and erosive lesions for chronic LDA or NSAID users in OGIB cases by CE, respectively. Collectively, 19.3% of the cases were diagnosed with mucosal lesions with long-term LDA or NSAID treatment in OGIB cases by CE. The prevalence of NSAID-induced mucosal injury among chronic NSAID users has been reported in several studies. Small intestinal ulceration was found in 21 patients (8.4%) among 249 long-term NSAID users and just 3 patients (0.6%) among 464 non-users in a previous investigation where the stomach, duodenum, and small intestine of 713 post-mortem patients were examined (16). Another recent study using video capsule endoscopy has demonstrated occurrence of small bowel injury in 71% of NSAID users compared with
The clinical features of NSAID-induced small bowel lesions have been documented. Hayashi et al. analyzed 7 patients with small bowel lesions while taking NSAIDs out of 61 patients who had undergone BE for OGIB. The results have shown that ulcers or erosions were observed in the ileum in six patients (86%) and in the jejunum in one patient (14%). Another recent report has shown that 12 (57.1%) out of 21 small bowel lesions in chronic NSAID users were found in the ileum. On the other hand, investigating the distribution of CE-detected small bowel lesions revealed that the lesions were found in the proximal, middle, and distal small bowel, suggesting that there were no significant tendencies in the distribution of small bowel lesions. The distribution and types of small intestinal injury due to NSAIDs have been studied, and it has been shown that in the majority of denuded areas located in the proximal part, erosions were found throughout the small intestine, and all of the ulcers were in the distal part, suggesting that the distribution differed according to the type of mucosal injury during short-term NSAID medication. Our results demonstrate differences in the distribution between ulcers and erosion in patients taking long-term LDA or NSAIDs, indicating that ulcers are located mainly in the ileum and were found in the ileum, whereas erosions were located throughout the small intestine.

LDA is used as a preventive treatment for ischemic heart disease and ischemic cerebrovascular disease. Recent reports have indicated that low-dose aspirin causes not only gastroduodenal mucosal injury but also small bowel injury with high frequency. Hayashi et al. have reported that 8 (44%) of 18 patients diagnosed with NSAID-induced small bowel injury by DBE were taking low-dose aspirin. Watanabe et al. have investigated small bowel injury with CE in 11 patients who developed gastric ulcers while undergoing low-dose aspirin. The study showed that red spots were found in 100% of the patients and mucosal breaks were found in 90.9% of the patients, indicating that very high incidences of small bowel injury were found in the patients who developed gastric ulcers while undergoing low-dose aspirin treatment. In our results, there were more patients taking LDA in the erosion cases than in the ulcer cases, suggesting the possibility that the characteristic endoscopic features of LDA-induced mucosal injury in the small intestine were smaller in size than in the case of NSAID-induced mucosal injury.

It has been demonstrated that co-administration of prostaglandin and rebamipide reduced the incidence of NSAID-induced small intestinal lesions. In our study, NSAIDs were withdrawn if possible. However, in some cases, especially in the case of LDA and the anti-platelet drug, thienopyridine, it was not possible to withdraw the LDA. In these cases, the prostaglandin or rebamipide was used concomitantly and has shown improved clinical course or CE findings after the treatment. These findings suggest that prostaglandin or rebamipide is effective for treating LDA or NSAID-induced mucosal injury of the small intestine.

In conclusion, our CE study demonstrated that erosive lesions were located in the entire small intestine (jejunum and ileum), and such lesions were observed predominantly in chronic LDA users. In contrast, ulcerative lesions were located mainly in the ileum and were found in NSAID users. However, concomitant use of thienopyridine such as clopidogrel with LDA appeared to increase ulcerative lesions in patients without using

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**Table 1** Details of the characteristics of ulcerative lesions in chronic non-steroidal anti-inflammatory drug users

| Age | Gender | UD | Species (duration) | Symptom | Hemoglobin (g/dL) | Location | Number | Treatment | Clinical course |
|-----|--------|----|--------------------|---------|------------------|----------|--------|-----------|---------------|
| 67  | F      |     | Loxoprofen (6M)    | Tarry stool/anemia | 9.5   | Ileum | Multiple | Withdrawal of NSAID | Improved |
| 83  | M      | OD  | Diclofenac (6M)    | FOBT (+) anemia    | 11.5  | Jejunum Ileum | Multiple | Withdrawal of NSAID | Improved |
| 59  | M      | ID  | LDA + clopidogrel (6M) | Tarry stool/anemia | 10.3  | Ileum | Multiple | Withdrawal of NSAID | Improved |
| 70  | M      | CD  | LDA + clopidogrel (2Y) | Tarry stool/anemia | 9.3   | Jejunum Ileum | Multiple | Continuation of NSAID | Improved |
| 79  | F      | RA  | Diclofenac (4Y)    | Tarry stool/anemia | 8.3   | Ileum | Multiple | Continuation of NSAID | Improved |
| 74  | F      | ID  | LDA + clopidogrel (1Y) | Anemia/abdominal pain | 9.3   | Ileum | Multiple | Withdrawal of NSAID | Improved |
| 63  | M      | OD  | Loxoprofen (6Y)    | Tarry stool/anemia | 11.2  | Ileum | Multiple | Withdrawal of NSAID | Improved |
| 73  | F      | OD  | Diclofenac (5Y)    | Tarry stool/anemia | 10.4  | Ileum | Multiple | Withdrawal of NSAID | Improved |

UD: Underlying diseases; OD: Orthopedic diseases; ID: Ischemic heart diseases; CD: Cerebrovascular diseases; RA: Rheumatoid arthritis; LDA: Low-dose aspirin; NSAID: Non-steroidal anti-inflammatory drug.
NSAIDs, which suggests that small-bowel mucosal injuries can be changed from LDA type to NSAID type by the additional use of anti-platelet drugs.

**COMMENTS**

**Background**

It has been demonstrated that low-dose aspirin (LDA) and non-steroidal anti-inflammatory drugs (NSAIDs) increase the risk of gastroduodenal mucosal injury.

**Research frontiers**

Recent reports have indicated that low-dose aspirin causes not only gastroduodenal mucosal injury but also small bowel injury with high frequency.

**Innovations and breakthroughs**

It has been demonstrated that co-administration of prostaglandin and rebamipide reduced the incidence of NSAID-induced small intestinal lesions24,25. In this study, NSAIDs were withdrawn if possible.

**Applications**

The concomitant use of anti-platelet drugs with LDA tends to exacerbate the study, NSAIDs were withdrawn if possible. The incidence of NSAID-induced small intestinal lesions is reduced by total enteroscopy with a non-invasive therapeutic procedure.

**Peer review**

This retrospective study analyzed the clinical feature of small intestinal mucosal lesion of the chronic NSAIDs users in the cases of obscure gastrointestinal bleeding.

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P- Reviewer: Calabrese C, Holt RJ, Koulaouzidis A
S- Editor: Qi Y  L- Editor: A  E- Editor: Wang CH
