Adverse Effects of Low-Dose Aspirin in the Gastrointestinal Tract

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Katsunori Iijima

Introduction

Aspirin is widely administered at relatively low doses (75–325 mg/day) as an antithrombotic drug to prevent cerebrovascular and cardiovascular disease. However, aspirin, even at low doses, exerts adverse effects on the gastrointestinal (GI) tract through its pharmacological inhibitory action on cyclooxygenase (COX), which leads to GI tract ulcers and GI tract bleeding. Low-dose aspirin (LDA)-induced upper GI tract injury has received much attention [1, 2]. However, currently, although upper GI bleeding is decreasing, lower GI bleeding is increasing [3, 4], and renewed attention is focused on mucosal injury in the more distal sites (small and large intestine). Because the prevalence of serious GI adverse events, such as GI bleeding, is considerably low [5], identifying potential risk factors is important for establishing an efficient preventive strategy for long-term LDA users. In this chapter, LDA-induced adverse effects on the upper and lower GI tract are briefly reviewed regarding their pathogenesis, epidemiology, risk factors, and prevention.

K. Iijima, M.D. (✉)
Department of Gastroenterology, Akita University Graduate School of Medicine, 1-1-1 Hondo, Akita, Akita 010-8543, Japan
e-mail: kiijima@med.akita-u.ac.jp

Upper GI Tract Injury

Pathogenesis

Aspirin induces gastroduodenal mucosal injury through topical irritation or systemic effects through the inhibition of COX-1, which regulates prostaglandin biosynthesis from arachidonic acid. However, enteric-coated aspirin, which is designed to reduce local damage, has failed to show any clear benefit over uncoated LDA for reducing upper GI bleeding [6, 7], suggesting that the systemic effects, rather than the topical actions, are mainly involved in the pathogenesis of LDA-induced gastroduodenal lesions. The depletion of mucosal prostaglandin induced via the pharmacological action of aspirin results in impaired epithelial defenses, such as impaired gastric mucus secretion [8, 9], because prostaglandin in the gastroduodenal mucosa plays a central role in controlling the epithelial defense mechanism [10, 11]. Gastric acid is likely to exacerbate aspirin-induced injury through HCl back diffusion, resulting in the formation of a deeper injury [12, 13]. An essential role of gastric acid in LDA-induced gastroduodenal injury is supported by the preventive effect of a potent inhibitor of gastric acid secretion, a proton pump inhibitor (PPI), on aspirin-induced gastroduodenal mucosal injury [14]. In addition, aspirin induces the adhesion of neutrophils to endothelial cells within the mucosal capillaries

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by increasing intracellular adhesion molecule-1 (ICAM-1) expression, resulting in reduced blood flow with ischemic changes [15, 16].

Epidemiology

LDA induces a variety of upper GI adverse events, ranging from dyspeptic symptoms without macroscopic lesions to complicated peptic ulcers (bleeding and perforation) and even death.

Upper GI symptoms are common in LDA users, with a prevalence of up to 15–20 % of all such patients [17–19]. The extent and severity of endoscopic mucosal damage are not directly associated with an increased risk for dyspeptic symptoms [1, 19, 20]. Dyspepsia is not life threatening, but it can be a serious problem because it may decrease adherence to LDA due to troublesome symptoms [17]. Constant administration of LDA is a critical issue because the cessation of LDA is a significant risk factor for adverse cardiovascular events [18].

Endoscopic controlled studies have revealed that a variety of severe gastroduodenal mucosal injury, including petechiases, erosions, and ulcers, can be induced by LDA administration. Erosive lesions are frequently seen in up to 60 % of LDA users [19, 20]. In a recent, large-scale prospective study comprising 1454 LDA users in Japan, the prevalence of gastroduodenal erosions was reported to be 29.2 % [21]. In addition, the prevalence of gastroduodenal ulcers ranged from 5 to 30 % [19, 20]. The wide range of prevalence of LDA-induced gastroduodenal erosions and/or ulcers is partly due to the geographic differences resulting from the diverse effects of *H. pylori* infection on gastroduodenal lesions, such that the prevalence is higher in Western countries than that in Asia [22], or to the timing of the endoscopic examination. Notably, only 20 % of gastroduodenal ulcers were associated with the manifestation of dyspeptic symptoms[1]; thus, the clinical significance for the majority of asymptomatic erosions or ulcers is obscure because such tiny lesions likely heal spontaneously over a period of time.

Relatively few gastroduodenal ulcers lead to ulcer complications (bleeding or perforation) that could be life threatening. The annual incidence rate of major GI bleeding in a double-blind randomized, placebo-controlled trial of LDA users ranged from 0.07 to 1.57 %, and the relative risk of major GI bleeding in LDA users in relation to controls ranges from 1.5 to 2.6 [5, 19]. Perforation is also a rare event in LDA users, with an incidence of 32.7 per 100,000 patient-years in patients older than 65 years [19, 20].

Risk Factors

Because of the large number of patients taking LDA to prevent cerebrovascular and cardiovascular diseases and the relatively rare incident rate of complicated upper GI adverse events in aspirin users, identifying high-risk groups for upper GI adverse events from LDA users and targeting them as a prevention therapy should be an effective strategy [23].

A history of peptic ulcer, particularly associated complicated (bleeding or perforated) ulcers, is the most important risk factor for gastroduodenal adverse events in LDA users. Previous observational studies have indicated that a history of peptic ulcers increases the risk of the upper GI complication by approximately two- to threefold, and for a history of complicated peptic ulcers, the risk further increased five- to sixfold compared with the absence of such histories [24–26].

Older age (60 year or more) is generally considered a risk factor for gastroduodenal complications in patients taking LDA, although there are few studies to support this indication [23]. Otherwise, general comorbid diseases accompanied by aging rather than aging itself may be a therapeutic target for prevention in LDA users because after ulcers start bleeding, the comorbidity is associated with a fatal condition in peptic ulcer bleeding [27, 28].

The concomitant usage of some other drugs enhances LDA-induced upper GI adverse events.

To date, it has been established that co-prescribed nonaspirin nonsteroidal anti-inflammatory drugs (NSAIDs), including COX-2-selective inhibitors, antiplatelet agents, anticoagulants, and oral corticosteroids, increase the risk of adverse upper GI events in LDA users compared with monotherapy [23–26]. The interactions between these drugs and LDA were confirmed not only by many observational studies but also by more recent large-scale analyses using a network of healthcare databases [29, 30]. Because most of these drugs have injurious effects on the upper GI mucosa, it is not surprising that the concomitant use of these drugs exacerbates LDA-induced upper GI mucosal injury.

For the interaction between *H. pylori* infection and LDA use, thus far, observational studies have shown conflicting results, with some showing an additive effect, others showing antagonizing effects, and still others showing no overall interaction [23]. A recent systematic review of *H. pylori* and the risk of upper GI bleeding in aspirin users concluded that the current data are not sufficient to allow a meta-analysis of the issue [31]. A series of recent studies in which individual gastric acid secretion levels were measured in chronic LDA users indicated that *H. pylori* infection could have biphasic effects on drug-induced gastroduodenal injury, depending on the gastric acid secretion level. The infection exacerbates mucosal injury in the presence of sufficient gastric acid, whereas the infection protects the mucosa from injury through a hypochlorhydric state accompanied by the infection [32–35]. In patients with *H. pylori* infection, evaluation of serum pepsinogen levels or endoscopic findings prior to the commencement of aspirin administration may help identify a high-risk group for upper GI adverse events from LDA users by extracting hyperchlorhydric subjects [32, 33].

Prevention

According to several guidelines [36, 37], patients with the above risk factors for upper GI bleeding must be coadministered preventive gastroprotective drugs when LDA is started.

The effectiveness of potent antisecretory drugs, PPIs, on upper GI adverse events in LDA users has been consistently reported in several randomized controlled trials [38–40]; PPIs completely prevent the recurrence of upper GI events in LDA users, even in high-risk groups with histories of complicated peptic ulcers [14]. Therefore, co-therapy with PPIs is recommended for LDA users with risk factors based on an expert consensus [36, 37], and prevention therapy is broadly implemented in clinical practice. In addition, PPIs may be effective in alleviating dyspeptic symptoms, even in the absence of endoscopic abnormality [41, 42], which could boost patient compliance with LDA treatment. Therefore, the broader application of PPIs to a wide range of LDA users, regardless of the presence or absence of accompanying risk factors, would be an alternative strategy for managing aspirin users in the expectation of boosting patient adherence to long-term LDA treatment [14]. However, other than the cost-effectiveness of the broader application of PPIs, recent studies in animal models and humans have indicated that PPI administration may enhance LDA-induced mucosal injury at more distal sites (small intestine) instead of preventing gastroduodenal mucosal injury, as discussed below. Hence, preventive therapy with PPIs should remain targeted to LDA users with risk factors.

By contrast, although a previous study indicated the significant effectiveness of a histamine H_2 receptor antagonist (H2RA) on upper GI adverse events in LDA users compared to placebo [43], other studies have demonstrated that the preventive effect by H2RA is significantly inferior to that of PPIs [44, 45]. Therefore, co-therapy with H2RA is unsatisfactory for the prevention of adverse upper GI events in LDA users.

Misoprostol, a prostaglandin E1 analogue, shows preventive effects on NSAID-induced gastroduodenal mucosal injury, although the use of the drug was restricted due to its severe abdominal side effects, such as diarrhea and

nausea. However, a previous study demonstrated that a lower dose of misoprostol (100 mg/day) significantly reduces gastroduodenal mucosal injury in LDA users without any abdominal side effects [46]. Rebamipide, a drug that stimulates gastric mucosal prostaglandin E1 and enhances the accompanying gastric mucus secretion [47, 48], also has potential effectiveness in the prevention of LDA-induced gastroduodenal mucosal injury without any serious side effects [49, 50]. However, these are small and explorative studies, and large-scale, clinical studies are required to introduce misoprostol or rebamipide in the clinical setting for the prevention of LDA-induced gastroduodenal mucosal injury.

H. pylori eradication therapy should be considered in *H. pylori*-positive LDA users with a history of peptic ulcers because a recent study indicated the long-term efficacy of the treatment for the recurrence of ulcer complications [51], as recommended by a recent European guideline on the management of *H. pylori* infection [52]. By contrast, the efficacy of eradication therapy for adverse gastroduodenal events in the remaining unselected *H. pylori*-positive LDA users without a history of peptic ulcers remains to be clarified [23]. This issue has significant implications in countries where the *H. pylori* infection rate remains high in the elderly, who are occasionally subjected to daily LDA intake, although the *H. pylori* infection rate is decreasing worldwide.

Lower GI Tract Injury

Pathogenesis

NSAIDs/aspirin also injures the small and large intestines with both topical effects on the epithelium and systemic effects via the suppression of epithelial prostaglandin biosynthesis. The latter mechanism is primarily involved in aspirin-induced enteropathy. The pathogenesis of NSAIDs/aspirin is multifactorial, and the following factors may be involved in the manifestation of drug-induced enteropathy: increased intestinal permeability, decreased intestinal mucus secretion, neutrophil infiltration and accompanying free radial formation, and bacterial infection [53–55]. Increased intestinal permeability may allow bile acid, pancreatic juice, and bacteria to invade the intestinal epithelium, leading to the induction of an inflammatory reaction in the tissue [53–55]. Consequently, inflammation in the small intestine is frequently manifested as mucosal lesions, such as erosions and ulcers. A previous study demonstrated that NSAIDs do not induce small intestine injury in germ-free rats [56]; therefore, bacteria in the small intestine may play an essential role in the formation of the ultimate mucosal lesions.

Nonetheless, caution should be used when extrapolating these mechanisms to the pathogenesis of aspirin-induced enteropathy occurring in humans because the majority of findings are from NSAID-induced enteropathy in animal models. In fact, experimental animal studies showed that orally administered aspirin, even at large doses, does not induce mucosal injury in the small intestine [53–55]. The difference in susceptibility to small intestine injury between NSAIDs and aspirin may be due to the difference in exposure time to each drug in the small intestine because the enterohepatic circulation of NSAIDs results in multiple time exposures of small intestine to the drug, whereas there is little enterohepatic circulation for aspirin [53–55]. However, previous studies showed increased intestinal permeability in aspirin users, even at a low dose, in humans [57, 58]. Thus, LDA may induce small intestine mucosal injury via the same mechanism as ordinary NSAIDs.

Epidemiology

Until recently, it was believed that damage to the human GI tract by LDA is mainly confined to the upper portion of GI tract up to the duodenum because the drug is primarily absorbed in the stomach and duodenum and rarely reaches the small intestine. Consequently, epidemiological studies on LDA-associated lower GI tract adverse events were limited, although the upper GI tract has been extensively investigated. However, with the advent of capsule endoscopy and

double balloon enteroscopy, the presence of small bowel injury can now be observed. Since the first case report of severe enteropathy in a LDA user by Leung et al. in 2007 [59], LDA-induced mucosal injury of the lower GI tract has received a great deal of attention.

The causal relationship of LDA to small intestine mucosal injury was confirmed using capsule endoscopy in healthy volunteers, in whom the short-term (1–2 weeks) administration of LDA significantly increased small intestine lesions compared with controls [57, 60]. Several studies using capsule endoscopy revealed the high prevalence (80–100 %) of small intestine injury of any degree in chronic LDA users with a wide spectrum of lesions, including multiple petechiae, loss of villi, erosions, and ulcers, although each study included a small number of patients (10–30 patients) [54]. A portion of these lesions may contribute to the pathogenesis of unexplained iron deficiency anemia or hypoalbuminemia, both of which are significantly more frequently observed in chronic LDA users [61, 62]. However, the clinical significance of the remaining vast majority of small intestine lesions observed in LDA users remains uncertain; therefore, human studies on small intestinal mucosal injury in LDA users should be interpreted with caution.

Colonic diverticular bleeding is the most frequent cause of lower GI bleeding, constituting 40 % of episodes of severe hematochezia [63]. Several studies have indicated that LDA use is a significant increased risk factor for diverticular bleeding [64–66], and a recent meta-analysis confirmed this association [67]. LDA use may facilitate bleeding of the colonic diverticulum partly due to its antithrombotic property.

No previous study has investigated the prevalence of lower GI bleeding in LDA users. The incidence of lower GI bleeding is 20–80/100,000, based on some population-based studies from the USA, Spain, and Iceland [3, 63, 68]. Because LDA use is associated with an increased risk of lower GI bleeding, with an odds ratio of 2–3 [69], the incidence of lower GI bleeding in LDA users should be severalfold higher than in the general population; however, it remains considerably low, in contrast to the high prevalence of lower GI tract mucosal lesions in LDA users.

Risk Factors

Considering the relatively low prevalence of lower GI bleeding in chronic aspirin users, the identification of risk factors is important for targeting patients with a potential preventive therapy. However, the risk factors for lower GI tract injury in LDA users are only now being identified and thus remain largely unknown.

Using capsule endoscopy in 205 chronic LDA users, Endo et al. identified the use of enteric-coated aspirin and PPI use as independent risk factors for the presence of small intestinal mucosal breaks [70]. Enteric-coated aspirin is designed to dissolve in the proximal small intestine to prevent gastric damage; however, this formula may allow aspirin to contact the intestinal mucosa at a high concentration, resulting in exacerbation of small intestinal injury. By contrast, the finding that PPI use exacerbates small intestinal injury in LDA users is supported by animal model studies by Wallace et al., who found that PPI use provokes dysbiosis in the small intestine through potent suppression of gastric acid, leading to exacerbation of NSAID-induced mucosal injury at that site in rats [71]. More recently, two case-control studies with lower GI bleeding as a primary outcome reported conflicting results for the association between PPI use and lower GI bleeding in LDA users. Lanas et al. reported that PPI use is weakly but significantly associated with an increased risk of lower GI bleeding in NSAIDs and/or LDA users [69], whereas Nagata et al. demonstrated that PPI use was not associated with the risk of lower GI bleeding in the entire cohort and even among LDA users [72]. Whether PPI use paradoxically exacerbates small intestinal injury in LDA users but PPI effectively prevents upper GI mucosal injury is a critical issue to be solved when managing aspirin users. An additional high-quality study to determine the association between PPI use and small intestinal mucosal

injury in LDA users is required to establish a comprehensive strategy for the prevention of mucosal injury to the overall (upper and lower) GI tract.

Prevention

Recently, there have been some attempts to prevent LDA-induced small intestinal injury, although these studies are all small and explorative. Using capsule endoscopy, Watanabe et al. demonstrated that misoprostol is effective in reducing the number of mucosal breaks of the small intestine in chronic LDA users, although a substantial portion (3 of 11) of patients experienced severe side effects of misoprostol (diarrhea) and dropped out of the study [73]. Endo et al., using capsule endoscopy in randomized controlled trial, indicated that probiotic (*Lactobacillus casei*) administration significantly decreased the number of mucosal breaks of the small intestine in chronic LDA users, with no side effects of the probiotics during the study period of 3 months [74]. This result is supported by an animal model study that showed the effectiveness of probiotics (*Lactobacillus casei* strain Shirota) on indomethacin-induced small intestinal injury [75].

Some studies have demonstrated the effectiveness of rebamipide in prevention of small intestinal injury in LDA users. As discussed above, rebamipide may exert its beneficial effects on not only the gastroduodenal mucosa but also the small intestinal mucosa by increasing mucosal prostaglandin biosynthesis [47]. Mizukami et al., using capsule endoscopy in healthy volunteers, indicated the significant effectiveness of rebamipide in reducing the number of subjects with small intestinal mucosal breaks [76]. More recently, Watanabe et al. used capsule endoscopy in a randomized, double-blind placebo-controlled trial and demonstrated that a high dose of rebamipide, but not placebo, significantly decreased the number of mucosal breaks in the small intestine in chronic LDA users without any side effects [77]. These studies indicate that probiotics and rebamipide are promising agents to prevent LDA-induced small intestinal injury. However, the number and presence of mucosal breaks were defined as primary outcomes for these studies, and the clinical significance of these lesions remains obscure because of the high prevalence of these lesions in the small intestines of LDA users. Further studies are required to investigate the effectiveness of candidate drugs on LDA-related small intestinal adverse lesions using the more rigorous clinical outcomes, such as decreased GI bleeding.

By contrast, there is no established prophylaxis for lower GI bleeding, including diverticular bleeding, in LDA users at present. In particular, diverticular bleeding usually occurs in the absence of mucosal injury [78], and a different preventive strategy other than the administration of muco-protective drugs is required to reduce the risk of LDA-related diverticular bleeding.

Conclusion

A preventive strategy for LDA-induced upper GI adverse events is being established that targets high-risk patients with preventive co-therapy using PPI administration. However, the epidemiology, risk factors, and treatment for LDA-induced lower GI adverse events are largely unknown at present. Because the incidence of lower GI bleeding is increasing in LDA users but that of the upper GI bleeding is decreasing, a preventive strategy for drug-induced lower GI adverse events must be established immediately.

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