

Pleiotropic Effects of Proton Pump Inhibitors

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Prevention of NSAID-Induced Small Intestinal Mucosal Injury: Prophylactic Potential of Lansoprazole

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Summary Non-steroidal anti-inflammatory drugs (NSAIDs), which are used for the treatment of several inflammatory disorders including rheumatoid arthritis, are well known to cause gastroduodenal mucosal lesions as an adverse effect. Recently, the serious problem of NSAID-induced small intestinal damage has become a topic of great interest to gastroenterologists, since capsule endoscopy and double-balloon enteroscopy are available for the detection of small intestinal lesions. Such lesions have been of great concern in clinical settings, and their treatment and prevention must be devised as soon as possible. Proton pump inhibitors (PPI), such as lansoprazole and omeprazole, show a potent anti-secretory effect. PPIs also have a gastroprotective effect, independent of their anti-secretory actions, which is probably mediated by inhibition of neutrophil functions as well as antioxidant actions. Administration of lansoprazole reduced the severity of the intestinal lesions in a dose-dependent manner, but omeprazole had no effect. The amount of heme oxygenase-1 (HO-1) protein in the intestinal mucosa was significantly increased by lansoprazole, but not by omeprazole. These results suggest that lansoprazole, but not omeprazole, ameliorates indomethacin-induced small intestinal ulceration through upregulation of HO-1/carbon monoxide. Therefore, lansoprazole may be useful for preventing the adverse effects of NSAIDs not only in the stomach but also in the small intestine.

Key Words: NSAID, small intestinal injury, lansoprazole, PPI

Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) including indomethacin inhibit prostaglandin (PG) production at inflamed sites by the inhibition of cyclooxygenase

(COX). NSAIDs are thought to demonstrate their anti-inflammatory, antipyretic, analgesic, and anti-platelet aggregation effects through this process. NSAIDs have been used widely in internal medicine and orthopedic surgery. They have been used to treat febrile diseases, inflammatory diseases, arthritis, lower back pain, and collagen diseases and to prevent and treat cerebrovascular diseases and ischemic heart diseases. PG is an important mediator in the inflammatory response. It also plays an important role in maintaining the homeostasis of many tissues and organs

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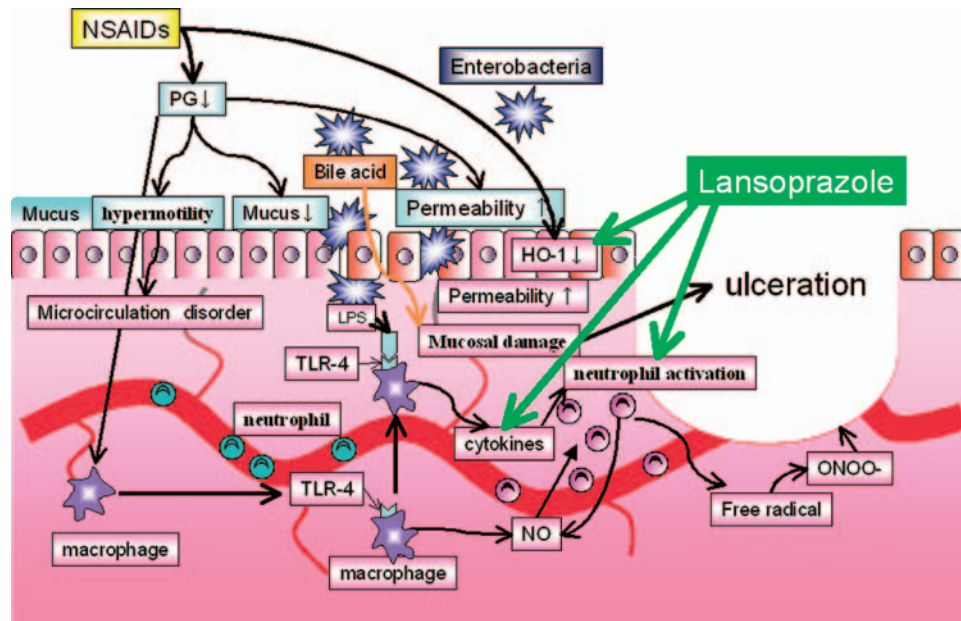


Fig. 1. Mechanisms of NSAID-associated small-bowel injury and the target points of lansoprazole in this mucosal injury. NSAIDs decrease the mucosal endogenous PG, resulting in the reduction of intestinal mucus, microcirculatory disturbances accompanying abnormally increased intestinal motility, the disruption of intercellular junctions and increased mucosal permeability. Mucosal injuries can be caused by the penetration of bile acid, proteolytic enzymes, intestinal bacteria, or toxins. At the same time, inflammatory cytokines are induced and neutrophil infiltration occurs. In addition, a pathway mediated by lipopolysaccharide (LPS)/toll-like receptor 4 (TLR4) plays an important role in the development of such injuries. Lansoprazole ameliorates such small intestinal ulceration through upregulation of HO-1/CO, the inhibition of inflammatory cytokines production and neutrophil infiltration.

including the gastrointestinal tract. When NSAIDs inhibit COX, they not only exhibit the expected anti-inflammatory effects but also could cause side effects such as gastrointestinal injury [1]. In our aging society, the use of NSAIDs has continued to increase, and their side effect of gastrointestinal mucosal injury has become a clinical problem.

Recently, the serious problem of NSAID-induced small intestinal damage has become a topic of great interest to gastroenterologists, since capsule endoscopy and double-balloon enteroscopy are available for the detection of small intestinal lesions [2–5]. Such lesions have been of great concern in clinical settings, and their treatment and prevention must be devised as soon as possible. In this report, we describe the mechanism and the strategy of NSAID-induced small bowel injury including prophylactic potential of lansoprazole.

Mechanisms of NSAID-associated Small Bowel Injury

First, elucidation of mechanism is necessary to devise measures for small-bowel injury due to NSAIDs. Much about this mechanism is unknown, but recently more information has become evident. A decrease in endogenous PG has been considered important in the development of NSAID-induced small-bowel injury [6]. PG is involved in

regulation of gastrointestinal blood flow and various mucosal functions such as increasing mucus secretion. Thus, the decrease in PG production is considered to be the main cause of small bowel injuries due to NSAIDs. In a rat study, exogenous PG administration was reported to markedly inhibit small bowel injuries induced by indomethacin, an NSAID. Besides the reduction of intestinal mucus, NSAIDs cause microcirculatory disturbances accompanying abnormally increased intestinal motility. Inflammatory cytokines are induced and neutrophil infiltration occurs. Then intestinal mucosal injuries can occur [7]. The involvement of NO derived from iNOS is also considered important in the development of such injuries [8–11].

Bjarnason *et al.* [12] stated that injury to small bowel mucosa involves the disruption of intercellular junctions, resulting in increased mucosal permeability. The disruption of intercellular junctions occurs because NSAIDs inhibit the production of mitochondrial ATP in intestinal epithelial cells. With increased mucosal permeability, mucosal injuries can be caused by the penetration of bile acid, proteolytic enzymes, intestinal bacteria, or toxins. Since indomethacin-induced small-bowel injuries do not develop in rats with germ-free intestines [13], the involvement of intestinal bacteria has been reported to be very important in such injuries. Watanabe *et al.* studied small bowel injuries

induced by indomethacin in rats. They reported that a pathway mediated by lipopolysaccharide (LPS)/toll-like receptor 4 (TLR4) plays an important role in the development of such injuries [14]. That is, NSAID-induced small-intestinal mucosal injuries begin with a PG decrease just as in NSAID-induced gastric mucosal injuries. Then mucosal protection declines and microcirculatory disturbances occur. Unlike gastric mucosal injuries, bacteria in the small intestine are thought to play an important role instead of gastric acid (Fig. 1). As mentioned before, NSAIDs inhibit mucosal PG synthesis by inhibiting COX activity. There are two types of COX: COX-1 and 2. In particular, COX-1 derived PG has been considered important in maintaining homeostasis of intestinal mucosa. In recent years, a study using an animal model has shown that small-intestinal mucosal injuries occurred only after both COX-1 and 2 were inhibited [15].

Prophylactic Potential of Lansoprazole to NSAID-induced Small Bowel Injury

PPI has a strong inhibitory effect on gastric acid secretion. PPI has been used widely in a clinical setting for *Helicobacter pylori* eradication and for the treatment of gastric ulcers, duodenal ulcers, reflux esophagitis and NSAID-induced gastric lesions [16–18]. PPI is also known to have protective effects on gastrointestinal mucosa without the inhibition of acid secretion [19–21]. These protective effects have been reported to occur via anti-inflammatory effects such as the inhibition of IL-8 production and neutrophil infiltration and via cell injury repair through MAPK [22–24]. A study was conducted using a rat model for small-intestinal mucosal injuries due to ischemia and reperfusion. Such injuries are said to involve neutrophils and reactive oxygen species. Lansoprazole inhibited small-intestinal mucosal injuries due to ischemia and perfusion via inhibition of neutrophils, lipid peroxidation, and inflammatory cytokine induction [25]. In addition, PPIs also reduced NSAID-induced small-intestinal mucosal injuries [26, 27].

We examined the effectiveness of lansoprazole compared with omeprazole. Male SD rats (200–300 g) were orally administered 10 mg/kg of indomethacin (IM) and small bowel injuries were created. Lansoprazole (30–100 mg/kg) inhibited small bowel injuries in a dose-dependent manner. Its effectiveness was significant at doses of 60 mg/kg or more, and the inhibition of 80% or more was observed at a dose of 100 mg/kg (Fig. 2) [28]. In contrast, omeprazole did not inhibit such injury at any of the tested doses (30–100 mg/kg). Pretreatment with lansoprazole inhibited the MPO activity and iNOS mRNA expression which were increased by indomethacin. The different effectiveness of lansoprazole compared with omeprazole cannot be fully explained by previously reported mechanisms [29–32].

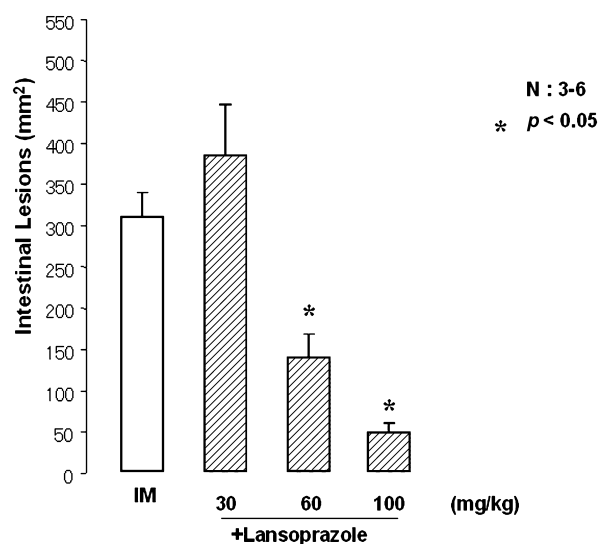


Fig. 2. Effects of lansoprazole on indomethacin-induced intestinal lesions in rats. Animals were given indomethacin (10 mg/kg, p.o.) and sacrificed 24 h later. Lansoprazole (30, 60, and 100 mg/kg) were given p.o. 30 min before the administration of indomethacin. Data are presented as the mean \pm SE from 6 rats. *Statistically significant difference from control (vehicle alone) at $p < 0.05$. Reprinted with permission [28].

An Anti-inflammatory Effect of Lansoprazole via Upregulation of HO-1/CO

The development of NSAID-induced ulcers cannot be explained by PG reduction alone. It has been recently reported that NSAID-induced cell death of gastric mucosa is necessary in the mechanism of NSAID-associated gastric mucosal injury [33, 34]. NSAIDs induce heme oxygenase-1 (HO-1) and this induction inhibits NSAID-dependent cell death. HO-1 is also called heat shock protein 32 (HSP 32) and is the rate limiting enzyme of heme metabolism. It degrades free heme which has high cytotoxicity. This degradation produces highly cytoprotective carbon monoxide (CO) and biliverdin, resulting in a cytoprotective effect [35–37] (Fig. 3). In recent years, CO has been reported to demonstrate a strong anti-inflammatory effect. CO has shown this effect by p38 MAP kinase activation, inhibiting the production of inflammatory cytokines, such as TNF- α and IL-1 β , and inducing the production of anti-inflammatory cytokine, IL-10 [38–40].

Mizushima *et al.* [41]. reported the following three points. NSAID-induced cell death of gastric mucosa is essential in the development of NSAID-induced gastric ulcers. NSAIDs induce HO-1 *in vitro* and *in vivo* via Nrf2 activation. This induction inhibits NSAID-dependent cell death of gastric mucosa, resulting in the inhibition of the development of NSAID-induced ulcers. HO-1 expression is induced mainly

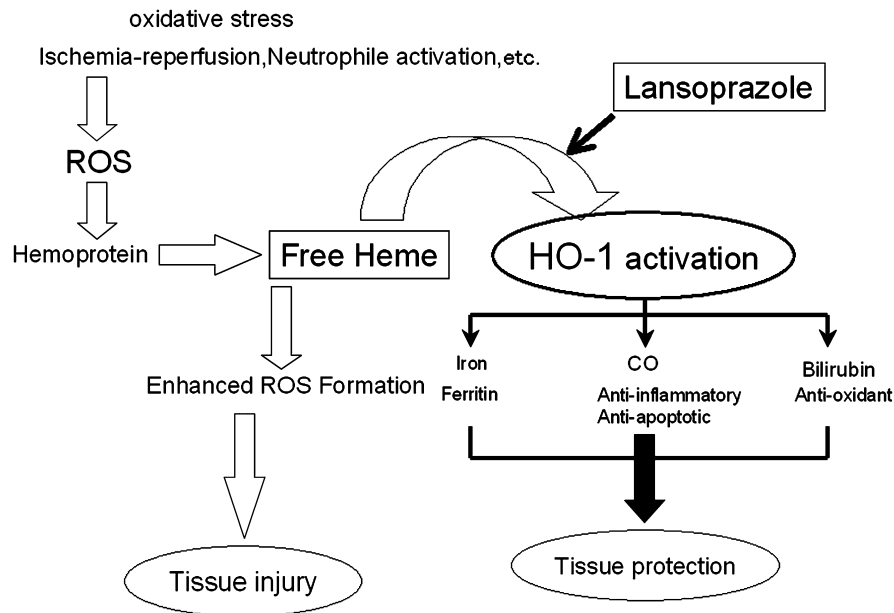


Fig. 3. Protective role of heme oxygenase-1 (HO-1) in oxidative tissue injuries. Oxidative stresses results in the production of free heme. Free heme is then involved in the generation of reactive oxygen species (ROS) further to increase oxidative stress. Induced HO-1 activity metabolizes free heme to iron, CO and biliverdin. Iron is directly sequestered and inactivated by co-induced ferritin. Biliverdin is rapidly converted to bilirubin by biliverdin reductase, and both bile pigments serve as a major anti-oxidant. CO can suppress cell apoptosis via the activation of p38 MAPK. In addition, HO-1 is also induced by pharmacological treatment, such as lansoprazole. Thus, HO-1 is an essential cytoprotective component against oxidative tissue injuries.

in macrophage cell lines and vascular endothelial cells under various stresses such as exposure to heavy metals and active oxygen species. When there is an increase in heme degradation by HO-1, cytoprotection occurs by the biochemical actions of various resulting degradation products [42, 43]. In addition, lansoprazole has been reported to induce HO-1 [44], and thus, HO-1 is thought to be involved in the inhibition of NSAID-associated small bowel injuries. We intravenously administered an HO-1 inhibitor SnPP (30 mg/kg) in rats [45]. It was administered 10 min before indomethacin administration. Pretreatment with SnPP aggravated small bowel injuries induced by indomethacin. On the contrary, pretreatment with both lansoprazole (100 mg/kg) and SnPP clearly aggravated mucosal injuries. HO-1 expression was examined using an ELISA kit (Stressgen, Rat HO-1 ELISA Kit) and immunoreaction. HO-1 is usually not expressed in normal rats. It was expressed in the mucosal epithelium 6 h after indomethacin (10 mg/kg) and lansoprazole (100 mg/kg) administrations. These results suggested that HO-1 is involved in the mechanism for inhibiting indomethacin-induced small bowel injuries using lansoprazole. CORM-2 (10 mg/kg) was administered intraperitoneally 30 min before and 6 h after indomethacin administration. Indomethacin-induced small bowel injuries were markedly inhibited. iNOS mRNA expression was also inhibited 6 h after indomethacin administration. In a recent study, CO released by CORM-2 was reported to inhibit NO and TNF- α production in mice

[46, 47]. There has been a report indicating that CO has an anti-inflammatory effect in DLD-1, a human colorectal cancer cell line [48]. Another report indicated that CO has an anti-inflammatory effect by inhibiting NF κ B activity [49, 50]. Still another report showed that indomethacin activates NF κ B in the small intestine, and the immunosuppressant tacrolimus inhibits NF κ B activity [51]. Thus, lansoprazole inhibits NF κ B activity via upregulation of HO-1/CO, suggesting the possible involvement of iNOS inhibition.

Conclusion

We have described the mechanism of and potential measures for NSAID-induced small-bowel injuries. The whole gastrointestinal tract must be managed in this era of increasing NSAID use. In considering this point, we can say that lansoprazole is a useful drug that can potentially protect the stomach and small intestine. We hope to examine these issues in future clinical studies.

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