Does Rebamipide Prevent Gastric Mucosal Injury in Patients Taking Aspirin and Clopidogrel?

Mitsushige Sugimoto · Takahiro Uotani ·
Takahisa Furuta

Received: 26 March 2014 / Accepted: 27 March 2014 / Published online: 8 April 2014
© Springer Science+Business Media New York 2014

The use of anti-platelet agents, such as low-dose aspirin (LDA) and clopidogrel, for primary and secondary prophylaxis against cardiovascular and cerebrovascular disease is increasing in an aging society, especially in developed countries. Moreover, since the benefits of dual anti-platelet therapy (DAT) with LDA and clopidogrel have been confirmed in the treatment or prevention of cardiovascular and cerebrovascular disease, DAT, but not monotherapy with LDA or clopidogrel, is often used in complicated patients such as after drug-eluting stent implantation, where DAT therapy is required for more than 6 months in order to avoid potentially catastrophic stent thrombosis. The efficacy of DAT for patients with a past history of cardiovascular events is well supported in the medical literature.

The downside of DAT is foregut mucosal injury, which affects almost all recipients, regardless of symptoms [1–3]. Thus, much attention has been focused on the prevention of mucosal injury, which can manifest as severe gastrointestinal hemorrhage or perforation. Accordingly, Tozawa et al. [4] in this issue of *Digestive Diseases and Sciences* demonstrated that in a randomized, double-blinded, placebo-controlled trial, rebamipide, a foregut mucosal protective agent widely used in Japan, significantly inhibited gastric mucosal damage induced by LDA alone or by DAT in healthy subjects.

The doses of anti-thrombotic agents are balanced between their beneficial and their adverse gastrointestinal effects, informed in part by their mechanisms of action. LDA, a platelet cyclooxygenase-1 inhibitor, not only injures the gastric mucosa, but also injures the esophageal and small bowel mucosa, even with enteric-coated formulations [2, 5]. The recommended doses of aspirin for the prevention of cardiovascular and cerebrovascular disease are 75–300 mg/day, though when benefits and adverse risks are taken into account, the optimal dose of aspirin is no more than 100 mg/day [6]. A gastric mucosal damage score of >1 according to the modified Lanza criteria [7] is observed in 93 % of healthy volunteers after administration of LDA, irrespective of age and duration of therapy [2]. Nevertheless, although the detailed biological mechanism of clopidogrel-induced mucosal damage is unclear, clopidogrel is less likely than LDA to damage the foregut mucosa, which belies the observation that clopidogrel often causes massive gastrointestinal bleeding due to its potent anti-platelet effects by the inhibition of the purinergic P2Y₁₂ receptor expressed on the platelet cell membrane [8]. This observation is supported in a separate analysis, in analyses divided modified Lanza scores into ulcer/erosion and hemorrhage scores in subjects receiving monotherapy with LDA or clopidogrel monotherapy, the former increasing both scores, yet the latter increased the hemorrhage score more than the ulcer/erosion score [1]. Using Cox proportional hazard regression analysis, monotherapy of clopidogrel increases the risk of upper gastrointestinal bleeding [hazard ratio 3.66; 95 % CI 2.96–4.51] [9] with the incidence of recurrent bleeding in clopidogrel users with a past history of bleeding from aspirin-induced ulcer 8.6 % (95 % CI 4.1–13.1 %) during 12 months of therapy [10]. Since more than 10 % of clopidogrel users with a past history of peptic ulcer experience recurrent ulceration [11],

M. Sugimoto (✉) · T. Uotani
First Department of Medicine, Hamamatsu University School of
Medicine, 1-20-1 Handayama, Higashi-ku,
Hamamatsu 431-3192, Japan
e-mail: mitsu@hama-med.ac.jp

T. Furuta
Center for Clinical Research, Hamamatsu University School of
Medicine, Shizuoka, Japan

clopidogrel-induced gastric mucosal damage is a problem to be reckoned with.

Risk factors of bleeding for LDA-induced gastric mucosal damage include older age, concomitant treatment with any kind of anti-coagulant therapy, nonsteroidal anti-inflammatory drugs (NSAIDs)/LDA, *H. pylori* infection and past history of peptic ulcer hemorrhage. Therefore, patients treated with DAT have an increased risk of upper gastrointestinal bleeding compared with patients treated with monotherapy with LDA or with clopidogrel. DAT induces gastric mucosal injury in more than 90 % of young, healthy, Japanese *H. pylori*-negative volunteers during 7 days of therapy [1]. Since the incidence and severity of DAT-induced gastric mucosal damage and bleeding have significant correlations with intragastric pH, use of proton pump inhibitors (PPIs) or histamine-2 receptor antagonists (H₂RA) is recommended to prevent and to treat drug-induced gastric mucosal damage and bleeding [12]. With clopidogrel and omeprazole cotherapy, the rate of overt upper gastrointestinal bleeding is significantly lower than with clopidogrel and placebo (HR 0.13, 95 % CI 0.03–0.56) [13]. In patients with a past history of peptic ulcer hemorrhage, the incidence of recurrent bleeding is 8.6 % (95 % CI 4.1–13.1 %) in clopidogrel users over 12 months and 0.7 % (95 % CI 0–2.0 %) in patients with LDA plus esomeprazole [10]. Moreover, co-administration of rabeprazole 10 mg effectively prevents DAT-induced gastric mucosal damage irrespective with *H. pylori* infection [1]. Yet, it is difficult to prevent DAT-induced gastric mucosal damage with standard-dose of PPI in all patients, especially in CYP2C19 rapid metabolizers [1]. Recently, the interaction between PPIs and clopidogrel has attracted much attention due to a recommendation from the US Food and Drug Administration (FDA) warning of possible harmful drug–drug interactions in which the therapeutic effects of clopidogrel are diminished by PPI therapy [14]. Therefore, alternative prophylactic regimens are desirable when clopidogrel is co-administered with LDA and/or PPIs.

Rebamipide (2-(4-chlorobenzoylamino)-3-[2-(1H)-quinolinon-4-yl]-propionic acid) is a major mucosal protective agent that defends the gastric mucosa from injury by increasing gastric mucus production, by increasing gastric mucosal blood flow, by stimulating the production of endogenous prostaglandins, and by decreasing the production of free oxyradicals. Of the biological activities of rebamipide, an increase in gastric mucosal blood flow and inhibition of lipid peroxidation mediated by oxygen radicals and activated neutrophils are especially important for the prevention of drug-induced gastric mucosal damage [15]. Several reports are available regarding the use of rebamipide in healthy subjects, patients and animal models of NSAID and aspirin drug-induced gastric mucosal injury.

In an animal model, rebamipide prevented DAT-induced gastric mucosal bleeding under conditions of acid secretion, although the effect is less pronounced than that of anti-secretory drugs [16]. In a randomized, double-blinded, placebo-controlled, crossover study, rebamipide 300 mg t.i.d. prevented LDA-induced gastric mucosal injury (i.e., erythema in the antrum) in healthy volunteers ($p = 0.039$) [3]. Moreover, rebamipide not only prevented LDA and NSAID-induced enteropathy, but also improved the nutritional status of the study subjects [17]. Nonetheless, it is unclear if rebamipide is useful for the prevention of gastric mucosal injuries induced by concomitant use of LDA and clopidogrel. Tozawa et al. [4] provide the first report of this nature in which they studied the protective effect of rebamipide on LDA- or DAT-related gastric mucosal damage using a randomized, double-blinded, placebo-controlled study design. Although treatment with LDA or DAT significantly aggravated gastric mucosal damage at day 14, co-administration of rebamipide significantly reduced the severity according to the modified Lanza score in subjects receiving LDA monotherapy or DAT ($p < 0.05$) [4]. Since many patients undergoing treatment with monotherapy and with DAT are asymptomatic [3], unexpected emergency hospitalization due to bleeding and abdominal symptoms is a serious problem in patients. In the Tozawa study, most subjects were asymptomatic, with no correlation between the gastrointestinal symptom rating scale and the modified Lanza score [4] supporting this observation.

In conclusion, Tozawa et al. [4] clearly demonstrated that rebamipide significantly inhibited gastric mucosal damage induced by LDA alone or by DAT in healthy subjects. These observations may suggest that rebamipide is useful for the primary prevention of LDA-induced gastric mucosal injury in low-risk subjects. Nevertheless, this study has the following limitations: most subjects were *H. pylori*-negative healthy volunteers and likely younger and healthier than typical patients undergoing DAT. Furthermore, the sample size was small and the study period was short in duration. Accordingly, this result should be considered preliminary, with further studies of a larger and more realistic population with a longer duration of therapy are required, incorporating a PPI arm so that rebamipide therapy can be directly compared with the current standard-of-care, PPI prophylaxis.

References

1. Uotani T, Sugimoto M, Nishino M, et al. Ability of rabeprazole to prevent gastric mucosal damage from clopidogrel and low doses of aspirin depends on CYP2C19 genotype. *Clin Gastroenterol Hepatol*. 2012;12:879–885.

2. Nishino M, Sugimoto M, Kodaira C, et al. Relationship between low-dose aspirin-induced gastric mucosal injury and intragastric pH in healthy volunteers. *Dig Dis Sci*. 2010;55:1627–1636.
3. Ono S, Kato M, Imai A, et al. Preliminary trial of rebamipide for prevention of low-dose aspirin-induced gastric injury in healthy subjects: a randomized, double-blind, placebo-controlled, cross-over study. *J Clin Biochem Nutr*. 2009;45:248–253.
4. Tozawa K, Oshima T, Okugawa T, et al. A randomized, double-blind, placebo-controlled study of rebamipide for gastric mucosal injury taking aspirin with or without clopidogrel. *Dig Dis Sci* (Epub ahead of print). doi: [10.1007/s10620-014-3108-4](https://doi.org/10.1007/s10620-014-3108-4).
5. Sugimoto M, Nishino M, Kodaira C, et al. Esophageal mucosal injury with low-dose aspirin and its prevention by rabeprazole. *J Clin Pharmacol*. 2010;50:320–330.
6. Cryer B, Feldman M. Effects of very low dose daily, long-term aspirin therapy on gastric, duodenal, and rectal prostaglandin levels and on mucosal injury in healthy humans. *Gastroenterology*. 1999;117:17–25.
7. Lanza FL. Endoscopic studies of gastric and duodenal injury after the use of ibuprofen, aspirin, and other nonsteroidal anti-inflammatory agents. *Am J Med*. 1984;77:19–24.
8. Fork FT, Lafolie P, Toth E, Lindgarde F. Gastroduodenal tolerance of 75 mg clopidogrel versus 325 mg aspirin in healthy volunteers. A gastroscopic study. *Scand J Gastroenterol*. 2000;35:464–469.
9. Lin CC, Hu HY, Luo JC, et al. Risk factors of gastrointestinal bleeding in clopidogrel users: a nationwide population-based study. *Aliment Pharmacol Ther*. 2013;38:1119–1128.
10. Chan FK, Ching JY, Hung LC, et al. Clopidogrel versus aspirin and esomeprazole to prevent recurrent ulcer bleeding. *N Engl J Med*. 2005;352:238–244.
11. Lai KC, Chu KM, Hui WM, et al. Esomeprazole with aspirin versus clopidogrel for prevention of recurrent gastrointestinal ulcer complications. *Clin Gastroenterol Hepatol*. 2006;4:860–865.
12. Taha AS, McCloskey C, Prasad R, Bezlyak V. Famotidine for the prevention of peptic ulcers and oesophagitis in patients taking low-dose aspirin (FAMOUS): a phase III, randomised, double-blind, placebo-controlled trial. *Lancet*. 2009;374:119–125.
13. Bhatt DL, Cryer BL, Contant CF, et al. Clopidogrel with or without omeprazole in coronary artery disease. *N Engl J Med*. 2010;363:1909–1917.
14. Depta JP, Bhatt DL. Antiplatelet therapy and proton pump inhibition: cause for concern? *Curr Opin Cardiol*. 2012;27:642–650.
15. Suzuki M, Miura S, Mori M, et al. Rebamipide, a novel antiulcer agent, attenuates *Helicobacter pylori* induced gastric mucosal cell injury associated with neutrophil derived oxidants. *Gut*. 1994;35:1375–1378.
16. Takayama S, Izuhara C, Yamada N, et al. A new model of gastric bleeding induced in rats by aspirin plus clopidogrel under stimulation of acid secretion. Prophylactic effects of antiulcer drugs. *J Physiol Pharmacol*. 2012;63:41–52.
17. Kurokawa S, Katsuki S, Fujita T, et al. A randomized, double-blinded, placebo-controlled, multicenter trial, healing effect of rebamipide in patients with low-dose aspirin and/or non-steroidal anti-inflammatory drug induced small bowel injury. *J Gastroenterol*. 2014;49:239–244.