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Gastroduodenal Mucosal Injury in Patients Taking Low-Dose Aspirin and the Role of Gastric Mucoprotective Drugs: Possible Effect of Rebamipide

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Summary **The present study was conducted to investigate the prevalence of mucosal injury in patients taking low-dose aspirin in Japan and examine the effect of gastric mucoprotective drugs on aspirin-related gastroduodenal toxicity. We selected 530 patients who had taken low-dose aspirin for 1 month or more after undergoing esophagogastroduodenoscopy from 2005 through 2006 at Teikyo University Hospital, Tokyo, Japan. Endoscopic records were retrospectively reviewed to determine the presence of massive bleeding and mucosal injury (ulcer or erosion). The influence of clinical factors, including co-administration of gastroprotective drugs, was also examined. Hemorrhage was observed in 25 patients (3.7%) and mucosal injury (36.2%) in 192 patients. The presence of *Helicobacter pylori* antibody was a significant risk factor associated with mucosal injury. Patients taking any gastroprotective drug showed a significantly lower rate of mucosal injury than those not taking these drugs. Patients taking rebamipide concomitantly with proton pump inhibitors or histamine 2 receptor antagonists had mucosal injury less frequently than those taking acid suppressants plus other mucoprotective drugs. In conclusion, these results show the possible gastroprotective effects of rebamipide, suggesting that it may be a good choice in aspirin users with gastroduodenal toxicity that is not suppressed by acid suppressants alone.**

Key Words**: aspirin, mucoprotective drug, acid suppressant, rebamipide**

Introduction

Gastrointestinal toxicity induced by non-steroidal anti-inflammatory drugs (NSAIDs) is one of the major causes of peptic ulcers. Due to its widespread use, low-dose aspirin (LDA), which is used for prophylaxis of atherothrombotic diseases, plays an important role in the occurrence of peptic ulcers. In Japan, administration of LDA has been rapidly increasing as the population ages.

Previous studies have shown that upper gastrointestinal bleeding caused by LDA can be decreased with acid suppressants, such as proton pump inhibitors (PPI). Unfortunately, these protective effects are incomplete, and new therapeutic options have not been developed [*1–4*]. Many gastroduodenal mucoprotective drugs have not been evaluated in terms of efficacy for LDA-related toxicity, although they are often used in clinical settings in Japan. In addition, there is little clinical information and the current condition of LDA-related gastrointestinal mucosal injury remains uncertain in Japanese subjects [*5*, *6*]. We conducted this study to clarify the current condition of mucosal injury in Japanese

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patients taking LDA and to identify potential effective treatments against LDA-induced mucosal injury.

Materials and Methods

This study involved a retrospective review of medical records. From January 2005 through December 2006, 5555 patients underwent upper gastrointestinal endoscopy at the Department of Internal Medicine of Teikyo University Hospital (Tokyo, Japan). Among these patients, 548 had taken LDA for 1 month or more and were selected for inclusion in this study. Patients with malignant diseases, hemorrhage from variceal lesions, and Mallory-Weiss syndrome were excluded because of difficulty in performing accurate endoscopic evaluations. Thus, 530 patients were enrolled as study subjects. All endoscopic examinations performed at this hospital are recorded with more than 20 photographs. Two well-trained examiners with more than 10 years' experience retrospectively evaluated endoscopic records to determine whether gastroduodenal mucosal injury and bleeding from the lesion were present; examiners were blinded to patient data. If the two examiners differed in opinion, another examiner evaluated the record again to make a final diagnosis. Bleeding was diagnosed on the basis of endoscopic evidence of current or recent hemorrhage with drop of hemoglobin of 2 g/dl or more, which was judged to require hospitalization. Minor hemorrhages judged to be treatable on an outpatient basis, such as small clots attached to the gastric wall, were not classified as "bleeding" in the present study. Mucosal injury was defined as obvious findings of gastroduodenal mucosal defects including both erosion (less than 5 mm in diameter) and ulcer (more than 5 mm).

Background characteristics of the subjects (age, gender, underlying disease, reason for undergoing examination, past history of gastroduodenal ulcer, and concomitant administration of warfarin, NSAIDs, PPI, histamine 2-receptor antagonists (H2RA), or other gastric mucoprotective (MP) agents) were ascertained from medical records. The presence of serum anti-*Helicobacter pylori* (*H. pylori*) antibody was tested using a commercially available kit (E-plate®, Eiken Chemical Co., Tokyo, Japan) in participants who gave written informed consent. Chart review was performed to confirm the present status of the infection in subjects that underwent past eradication treatment.

Unadjusted odds ratios (OR) and 95% confidence intervals (CI) were calculated to clarify the significance of differences between two groups, if appropriate. Prior to the study, the protocol was approved by the institutional review board of Teikyo University.

Results

Underlying diseases of subjects included ischemic heart disease (66%), cerebrovascular disease (30%), and systemic arteriosclerosis (8%). The influence of background characteristics on gastroduodenal bleeding and mucosal injury are shown in Tables 1 and 2. The only factor significantly associated with reduced bleeding was co-administration of a PPI. In terms of mucosal injury, use of a PPI decreased the prevalence of mucosal injury, whereas the presence of *H. pylori* increased the prevalence (Table 2). The impact of gastric protective medications on gastroduodenal toxicity is presented in Table 3. Compared to patients not receiving any gastroprotective medication, any treatment was associated with significantly lower rates of bleeding and mucosal injury

Table 1. Effect of baseline characteristics on gastroduodenal bleeding in patients taking low-dose aspirin

Baseline characteristics	Bleeding+ (n = 25)	Bleeding– (n = 505)	Odds ratio (95% CI)	p value
Age (years)	70.3 ± 11.6	69.5 ± 11.3		ns
Male	14	281	1.01	ns
Female	11	224	(0.73–3.27)	
H. pylori+	17	158	1.86	ns
H. pylori–	6	104	(0.71–4.88)	
PPI+	5	211	0.34	<0.05
PPI–	20	294	(0.12–0.94)	
History+	7	122	1.22	ns
History–	18	383	(0.49–2.99)	
NSAIDs+	1	23	0.87	ns
NSAIDs–	24	482	(0.11–6.74)	
AP or AC+	4	99	0.54	ns
AP or AC–	21	406	(0.09–2.10)	

p values were calculated with chi-square test or t test. Abbreviations: *H. pylori*, serum anti-*Helicobacter pylori* antibody; PPI, proton pump inhibitor; NSAIDs, nonsteroidal anti-inflammatory drugs; AP, anti-platelet agents; AC, anticoagulants.

Table 2. Effect of baseline characteristics on gastroduodenal mucosal injury in patients taking low-dose aspirin

Baseline characteristics	Mucosal injury+ (n = 192)	Mucosal injury– (n = 338)	Odds ratio (95% CI)	p value
Age (years)	69.2 ± 10.7	69.8 ± 11.6		ns
Male	113	182	1.2	ns
Female	79	156	(0.84–1.72)	
H. pylori+	93	82	2.14	<0.01
H. pylori–	38	72	(1.31–3.51)	
PPI+	51	165	0.38	<0.01
PPI–	141	173	(0.26–0.57)	
History+	53	76	1.3	ns
History–	139	262	(0.86–1.95)	
NSAIDs+	8	16	0.86	ns
NSAIDs–	184	322	(0.36–2.06)	
AP or AC+	48	85	0.99	ns
AP or AC–	144	253	(0.65–1.49)	

p values were calculated with chi-square test or t test. Abbreviations: *H. pylori*, serum anti-*Helicobacter pylori* antibody; PPI, proton pump inhibitor; NSAIDs, nonsteroidal anti-inflammatory drugs; AP, anti-platelet agents; AC, anticoagulants.

Table 3. Impact of gastroprotective medications on endoscopic findings

Treatment	Number	Bleeding	Mucosal injury	*H. pylori*
None	118	11 (9.3%)	58 (49.1%)	46/73 (63.0%)
Any medicine	412	14 (3.4%)**	134 (32.5%)**	129/222 (58.1%)
PPI	145	3 (2.1%)**	27 (18.6%)**	39/71 (54.9%)
H2RA	82	4 (4.9%)	33 (40.2%)	25/45 (55.6%)
MP	74	2 (2.6%)	38 (51.4%)	31/42 (73.8%)
PPI/H2RA + MP	111	5 (5.4%)	36 (32.4%)*	34/59 (57.6%)
Teprenone	33	2 (6%)	14 (42.4%)	12/20 (60.0%)
Rebamipide	27	0 (0%)	4 (14.8%)	7/13 (53.8%)
Ecabet sodium	14	2 (14.2%)	4 (28.6%)	2/8 (25.0%)
Polaprezinc	13	0 (0%)	4 (30.8%)	6/12 (50.0%)
Others[#]	26	1 (3.8%)	10 (38.5%)	7/11 (63.6%)
Total	530	25 (4.7%)	192 (36.0%)	175/295 (59.3%)

[#]sucralfate, aldioxa, cetraxate, sofalcone, and sodium alginate, all which were prescribed for less than 10 patients. *p<0.05, **p<0.01, compared with no-medication group (chi-square test). Abbreviations: PPI; proton pump inhibitor, H2RA; H2 receptor antagonist, MP; mucoprotective agent.

(p<0.01 for both comparisons). Similarly, use of a PPI alone was significantly more protective against bleeding and mucosal injury than non-use of any medicine (p<0.01 for both comparisons). In terms of combination therapy, patients taking a PPI or H2RA plus an MP agent showed significantly better outcomes in terms of mucosal injury compared to patients taking no medication. Use of a PPI/H2RA plus rebamipide was associated with a better overall outcome (bleeding, mucosal injury) than acid suppressants plus other MPs, although the rate of *H. pylori* infection, a significant confounding factor, did not differ between two groups (Table 4).

Discussion

Aspirin, even in low doses, induces gastrointestinal mucosal injury and hemorrhage, which limits its clinical use. LDA-induced gastrointestinal toxicity has become a big problem in Japan as well as other countries. A case-control study of hemorrhagic peptic ulcer patients indicated that the risk of LDA for bleeding from ulcers is similar to other NSAIDs [*7*]. Other reports also support the high prevalence of gastroduodenal mucosal injury in LDA users [*5*, *6*]. Although information is limited in Japanese patients, data indicate that effective treatments are needed for LDA-

Table 4. Impact of co-administration of acid suppressants and rebamipide on gastroduodenal injury

Treatment	Number	Bleeding	Mucosal injury		*H. pylori*
PPI + Reb	22	0	3 (1)		5/10 (50%)
H2RA + Reb	5	0	1 (0)		2/3 (66.7%)
Total	27	0	4 (1) (14.8%)		7/13 (53.8%)
PPI + MP	49	2	16 (1)	$p<0.05$*	18/35 (51.4%)
H2RA+MP	35	3	16 (4)		16/24 (66.7%)
Total	84	5	32 (5) (38.1%)		34/59 (57.6%)

*by chi-squered test. ( ); number of ulcer. Abbreviations: MP; mucoprotective agents other than rebamipide, PPI; proton pump inhibitor, H2RA; histamine 2 receptor antagonist, Reb; rebamipide.

related gastrointestinal toxicity in Japanese patients as well.

Previous studies support the avoidance of LDA when risks outweigh benefits [*8*]. However, in cases in which LDA use is required, such as after placement of a drug-eluted coronary stent, protection of gastrointestinal mucosa against LDA-injury is important. Proven treatment for LDA-related mucosal injury includes co-administration of a PPI and eradication of *H. pylori*. Because these treatments are comparable in efficacy, but do not provide complete protection, other therapeutic options are needed. Co-administration of acid suppressants and other gastroprotective medicines is one possible treatment, although we can find only one report regarding this treatment [*9*].

The present data clearly showed the effectiveness of acid suppressants, especially PPI, for suppressing LDA-induced mucosal damage, which is consistent with previous data [*6*]. Patients receiving any gastroprotective medicine suffered from mucosal injury significantly less frequently than those who did not receive any medication. In addition, acid suppressants plus rebamipide showed a trend of lowering gastroduodenal damage. This additive effect was not seen with other mucoprotective agents. Rebamipide provides it gastric mucoprotective effect via different mechanisms from acid suppressants, which affect not only the upper gastrointestinal tract but also other intestinal organs [*10–15*]. Rebamipide stimulates the production of prostaglandins and epidermal growth factor, preventing *H. pylori*-elicited neutrophil-induced mucosal injury and decreasing free radical levels [*16*, *17*]. Clinically, the efficacy against NSAID-induced gastric injury is reported as comparable to that of low-dose famotidine, one of H2RA [*18*]. The present results suggest the new potential for use of rebamipide with a PPI and H2RA to protect against LDA-related intestinal damage.

The limitations of the present study include the retrospective study design, the small sample number, and the fact that all patients were drawn from a single institute. Because selection bias may have affected the present results, data should be interpreted carefully. A prospective trial is needed to clarify the effect of rebamipide added to PPIs and H2RA therapy on the prevention of aspirin-induced GI injury.

References

[1] Chan, F.K., Chung, S.C., Suen, B.Y., Lee, Y.T., Leung, W.K., Leung, V.K., Wu, J.C., Lau, J.Y., Hui, Y., Lai, M.S., Chan, H.L., and Sung, J.J.: Preventing recurrent upper gastrointestinal bleeding in patients with *Helicobacter pylori* infection who are taking low-dose aspirin or naproxen. *N. Engl. J. Med.*, **344**, 967–973, 2001.

[2] Lai, K.C., Lam, S.K., Chu, K.M., Wong, B.C., Hui, W.M., Hu, W.H., Lau, G.K., Wong, W.M., Yuen, M.F., Chan, A.O., Lai, C.L., and Wong, J.: Lansoprazole for the prevention of recurrences of ulcer complications from long-term low-dose aspirin use. *N. Engl. J. Med.*, **346**, 2033–2038, 2002.

[3] Ibáñez, L., Vidal, X., Vendrell, L., Moretti, U., and Laporte, J.R., on behalf of the Spanish-Italian Collaborative Group for the Epidemiology of Gastrointestinal Bleeding.: Upper gastrointestinal bleeding associated with antiplatelet drug. *Aliment. Pharmacol. Ther.*, **23**, 235–242, 2006.

[4] Lanas, A., García-Rodríguez, L.A., Arroyo, M.T., Gomollón, F., Feu, F., González-Pérez, A., Zapata, E., Bástida, G., Rodrigo, L., Santolaria, S., Güell, M., de Argila, C.M., Quintero, E., Borda, F., and Piqué, J.M., on behalf of the Investigators of the Asociación Española de Gastroenterologia.: Risk of upper gastrointestinal ulcer bleeding associated with selective cyclo-oxygenase-2 inhibitors, traditional non-aspirin non-steroidal anti-inflammatory drugs, aspirin and combinations. *Gut*, **55**, 1731–1738, 2006.

[5] Yamamoto, T., Sanaka, M., Nagasawa, K., Abe, K., Fukami, M., Nakayama, S., Tsuchiya, A., Ishii, T., and Kuyama, Y.: Gastroduodenal mucosal injury in patients on antiplatelet therapy. *Thromb. Res.*, **120**, 465–469, 2007.

[6] Shiotani, A., Sakakibara, T., Yamanaka, Y., Imamura, H., Tarumi, K., Manabe, N., Kamada, T., Kusunoki, H., Hata, J., and Haruma, K.: Upper gastrointestinal ulcer in Japanese patients taking low-dose aspirin. *J. Gastroenterol.*, **44**, 126–131, 2009.

[7] Sakamoto, C., Sugano, K., Ota, S., Sakaki, N., Takahashi, S., Yoshida, Y., Tsukui, T., Osawa, H., Sakurai, Y., Yoshino, J.,

Mizokami, Y., Mine, T., Arakawa, T., Kuwayama, H., Saigenji, K., Yakabi, K., Chiba, T., Shimosegawa, T., Sheehan, J.E., Perez-Gutthann, S., Yamaguchi, T., Kaufman, D.W., Sato, T., Kubota, K., and Terano, A.: Case-control study on the association of upper gastrointestinal bleeding and non-steroidal anti-inflammatory drugs in Japan. *Eur. J. Clin. Pharmacol.*, **62**, 765–772, 2006.

[8] Patrono, C., Garcia Rodriguez, L.A., Landolfi, R., and Baigent, C.: Low-dose aspirin for the prevention of atherothrombosis. *N. Engl. J. Med.*, **353**, 2373–2383, 2005.

[9] Yilmaz, S., Bayan, K., Dursun, M., Canoruc, F., Kilinc, N., Tüzün, Y., Danis, R., and Ertem, M.: Does adding misoprostol to standard intravenous proton pump inhibitor protocol improve the outcome of aspirin/NSAID-induced upper gastrointestinal bleeding?: A randomized prospective study. *Dig. Dis. Sci.*, **52**, 110–118, 2007.

[10] Park, S.H., Cho, C.S., Lee, O.Y., Jun, J.B., Lin, S.R., Zhou, L.Y., Yuan, Y.Z., Li, Z.S., Hou, X.H., Zhao, H.C., Kachintorn, U., Kositchaiwat, C., and Lertkupinit, C.: Comparison of prevention of NSAID-induced gastrointestinal complications by rebamipide and misoprostol: a randomized, multicenter, controlled trial-STORM STUDY. *J. Clin. Biochem. Nutr.*, **40**, 148–155, 2007.

[11] Kim, H.K., Kim, J.I., Kim, J.K., Han, J.Y., Park, S.H., Choi, K.Y., and Chung, I.S.: Preventive effects of rebamipide on NSAID-induced gastric mucosal injury and reduction of gastric mucosal blood flow in healthy volunteers. *Dig. Dis. Sci.*, **52**, 1776–1782, 2007.

[12] Suzuki, T., Yoshida, N., Nakabe, N., Isozaki, Y., Kajikawa, H., Takagi, T., Handa, O., Kokura, S., Ichikawa, H., Naito, Y., Matsui, H., and Yoshikawa, T.: Prophylactic effect of rebamipide on aspirin-induced gastric lesions and disruption of tight junction protein zonula occludens-1 distribution. *J. Pharmacol. Sci.*, **106**, 469–477, 2008.

[13] Niwa, Y., Nakamura, M., Ohmiya, N., Maeda, O., Ando, T., Itoh, A., Hirooka, Y., and Goto, H.: Efficacy of rebamipide for diclofenac-induced small-intestinal mucosal injuries in healthy subjects: a prospective, randomized, double-blinded, placebo-controlled, cross-over study. *J. Gastroenterol.*, **43**, 270–276, 2008.

[14] Ono, S., Kato, M., Imai, A., Yoshida, T., Hirota, J., Hata, T., Takagi, K., Kamada, G., Ono, Y., Nakagawa, M., Nakagawa, S., Shimizu, Y., Takeda, H., and Asaka, M.: 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.*, **45**, 248–253, 2009.

[15] Iijima, K., Ichikawa, T., Okada, S., Ogawa, M., Koike, T., Ohara, S., and Shimosegawa, T.: Rebamipide, a cytoprotective drug, increases gastric mucus secretion in human: evaluations with endoscopic gastrin test. *Dig. Dis. Sci.*, **54**, 1500–1507, 2009.

[16] Terano, A., Arakawa, T., Sugiyama, T., Suzuki, H., Joh, T., Yoshikawa, T., Higuchi, K., Haruma, K., Murakami, K., Kobayashi, K., and for the Rebamipide Clinical Study Group.: Rebamipide, a gastro-protective and anti-inflammatory drug, promotes gastric ulcer healing following eradication therapy for *Helicobacter pylori* in a Japanese population: a randomized, double-blind, placebo-controlled trial. *J. Gastroenterol.*, **42**, 690–693, 2007.

[17] Nishizawa, T., Suzuki, H., Nakagawa, I., Minegishi, Y., Masaoka, T., Iwasaki, E., and Hibi, T.: Rebamipide-promoted restoration of gastric mucosal sonic hedgehog expression after early *Helicobacter pylori* eradication. *Digestion*, **79**, 259–262, 2009.

[18] Naito, Y., Iinuma, S., Yagi, N., Boku, Y., Imamoto, E., Takagi, T., Handa, O., Kokura, S., and Yoshikawa, T.: Prevention of indomethacin-induced gastric mucosal injury in *Helicobacter pylori*-negative healthy volunteers: A comparison study rebamipide vs famotidine. *J. Clin. Biochem. Nutr.*, **43**, 34–40, 2008.