Ability of Rabeprazole to Prevent Gastric Mucosal Damage From Clopidogrel and Low Doses of Aspirin Depends on *CYP2C19* Genotype

TAKAHIRO UOTANI,* MITSUSHIGE SUGIMOTO,* MASAFUMI NISHINO,* CHISE KODAIRA,* MIHOKO YAMADE,* SHU SAHARA,* TAKANORI YAMADA,* SATOSHI OSAWA,* KEN SUGIMOTO,* TATSUO TANAKA,‡ KAZUO UMEMURA,§ HIROSHI WATANABE,‖ HIROAKI MIYAJIMA,* and TAKAHISA FURUTA¶

**First Department of Medicine, ‡Department of Endoscopic and Photodynamic Medicine, §Department of Pharmacology, ‖Department of Clinical Pharmacology and Therapeutics, and ¶Center for Clinical Research, Hamamatsu University School of Medicine, Hamamatsu, Japan*

BACKGROUND & AIMS: Low doses of aspirin can injure the gastric mucosa. It is not clear whether other drugs such as the antiplatelet agent clopidogrel also cause gastric mucosal injury or exacerbate aspirin-induced injury, or whether proton pump inhibitors prevent damage. **METHODS:** Twenty Japanese subjects with different *CYP2C19* genotypes were randomly assigned to groups that were given a low dose of aspirin (100 mg; A), clopidogrel (75 mg; C), low dose of aspirin and clopidogrel (AC), or low dose of aspirin in combination with clopidogrel and rabeprazole (10 mg; ACR) once daily for 7 days. Subjects underwent gastroduodenoscopy and platelet tests on days 3 and 7; gastric mucosal damage was assessed by using the modified Lanza score (MLS). We performed 24-hour intragastric pH monitoring on day 7 of each regimen. We also analyzed the effects of the AC regimen on 30 patients with different *CYP2C19* genotypes. **RESULTS:** Subjects in groups A, C, and AC had significantly higher levels of gastric mucosal damage on days 3 and 7, compared with baseline. The median MLS for the AC group was similar to that of the A group. *Helicobacter pylori*–negative subjects in the ACR group with different *CYP2C19* genotypes had significant differences in MLS, intragastric pH, and platelet function. Gastric mucosal injury was inhibited equally among *H pylori*–positive subjects in the ACR group. Rabeprazole did not appear to affect platelet function or intragastric pH in subjects given clopidogrel. **CONCLUSIONS: Clopidogrel and low doses of aspirin cause a similar degree of gastric mucosal damage. Rabeprazole prevented this damage without reducing the antiplatelet function of clopidogrel. However, its prophylactic effect varies with *CYP2C19* genotype in *H pylori*–negative subjects.**

Keywords: Stomach; PPI; Drug Interactions; Cardiovascular.

Low-doses of aspirin (LDA), which have been used for primary and secondary prophylaxis against cardiovascular disorders, often causes gastrointestinal mucosal damage.[1–5] Although the risk of gastric mucosal damage by clopidogrel is reportedly lower in comparison with LDA,[6] clopidogrel sometimes causes massive gastrointestinal bleeding.[7] Moreover, it is unclear whether clopidogrel exacerbates LDA-induced gastric mucosal damage.

Prophylactic use of proton pump inhibitors (PPIs) is recommended for patients treated with dual antiplatelet regimens.[8] Clopidogrel and PPIs are mainly metabolized by S-mephenytoin 4′-hydroxylase (*CYP2C19*). The activity of *CYP2C19* is genetically classified into 3 groups, rapid metabolizers (RMs), intermediate metabolizers (IMs), and poor metabolizers (PMs).[9] Clinical effects of PPIs and clopidogrel significantly depend on *CYP2C19* genotype status.[9,10] Recently, there has been considerable concern regarding the interaction between PPIs and clopidogrel. Although PPIs were reported to diminish the antiplatelet effects of clopidogrel,[11] in a recent prospective study, the PPI did not increase the incidence of cardiovascular events in patients on clopidogrel therapy.[12]

Helicobacter pylori infection has been demonstrated to increase the risk of nonsteroidal anti-inflammatory drug (NSAID)–related and LDA-related gastric mucosal injury.[13] However, the effect of *H pylori* infection on gastric mucosa of patients treated with clopidogrel has not been made clear.

With the above-mentioned considerations in mind, we investigated the influence of clopidogrel on LDA-induced gastric mucosal damage, intragastric pH, platelet function, and abdominal symptoms with or without rabeprazole, a representative PPI, in relation to *CYP2C19* genotype status and *H pylori* infection.

Methods

Subjects

We recruited 118 healthy Japanese volunteers without any gastrointestinal symptoms such as heartburn or dyspepsia, after obtaining written informed consent. Exclusion criteria were past treatment for *H pylori* infection, history of peptic ulcer or abdominal operation, regular use of NSAIDs, LDA, clopidogrel, or any other medications, smoking, and age <20 years old.

The present study comprised 2 separate experiments. The first was designed to identify whether clopidogrel caused or exacerbated gastric mucosal damage, and whether rabeprazole effectively prevented gastric mucosal damage induced by dual therapy with LDA plus clopidogrel (study 1). The other explored whether gastric mucosal damage caused by dual therapy

Abbreviations used in this paper: **AC, aspirin and clopidogrel; ARU, aspirin reaction unit; *CYP2C19*, S-mephenytoin 4′-hydroxylase; GSRS, Gastrointestinal Symptom Rating Scale; IM, intermediate metabolizer; IPA, inhibition of platelet aggregation; LDA, low-dose aspirin; MLS, modified Lanza score; NSAID, nonsteroidal anti-inflammatory drug; PG, pepsinogen; PM, poor metabolizer; PPI, proton pump inhibitor; RM, rapid metabolizer; VN, Verify Now system.**

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with LDA and clopidogrel was affected by *CYP2C19* genotype status (study 2).

All subjects underwent gastroscopy, 24-hour intragastric pH monitoring, and platelet function tests to exclude severe gastroduodenal disorders, abnormal gastric acid secretion, or abnormal platelet function (control). We excluded 17 subjects because of moving away (n = 5), gastric erosions/duodenal ulcer (n = 4), use of medication (n = 3), withdrawal (n = 2), abnormal platelet function (n = 2), and gastrointestinal symptoms (n = 1). From the remaining 86 *H pylori*–negative subjects and 15 *H pylori*–positive subjects, we randomly selected 40 *H pylori*–negative subjects, comprising 10 subjects for study 1 (5 RMs and 5 IMs/PMs) and 30 subjects (10 RMs, 10 IMs, and 10 PMs) for study 2, and 10 *H pylori*–positive subjects (5 RMs and 5 IMs/PMs) for study 1 (Supplementary Table 1).

Study Protocol

Study 1 was conducted as a randomized, open-labeled, 4-way crossover study with 20 subjects (10 *H pylori*–positive and 10 negative subjects), who were administered the following: (1) aspirin 100 mg (Bayaspirin, enteric-coated aspirin tablet; Bayer Schering Pharma, Osaka, Japan) (A regimen); (2) clopidogrel 75 mg (Plavix; Sanofi-Aventis K.K., Tokyo, Japan) (C regimen); (3) aspirin 100 mg plus clopidogrel 75 mg (AC) regimen; and (4) aspirin 100 mg plus clopidogrel 75 mg plus rabepazole 10 mg (Pariet; Eisai Co Ltd, Tokyo, Japan) (ACR regimen).

In study 2, thirty subjects were administered the AC regimen for 7 days.

All study drugs (LDA, clopidogrel, and rabeprazole) were administered at 8:00 AM after breakfast. Subjects were not permitted alcohol or any other medications for at least 2 weeks before each regimen period and during the study period.

The washout period between regimens was at least 2 weeks, because esophageal and gastroduodenal mucosal damage resolved by 2 weeks after cessation of LDA in our previous study.[2,3,14] Gastroscopy and platelet function testing were performed on days 3 and 7 of each regimen. Symptom scoring and 24-hour intragastric pH monitoring were performed on day 7 of each regimen.

Approval for the study protocol was obtained in advance from the Human Institutional Review Board of the Hamamatsu University School of Medicine.

CYP2C19 *Genotyping,* Helicobacter pylori *Infection, and Pepsinogen Testing*

DNA was extracted from each subject's leukocytes by using a commercially available kit (Wizard Genomic DNA Purification Kit; Promega Corporation, Madison, WI). Subjects were classified into 3 genotype groups: RM (*1/1), IM (*1/2 or *1/3), and PM (*2/2, *2/3, or *3/3).

Screening for *H pylori* infection was conducted by using a serologic test (E plate Eiken *H pylori* antibody; Eiken Chemical, Co Ltd, Tochigi, Japan).

Gastroscopy

After an overnight fast, gastroscopy was performed by using an Olympus GIF-Q 260 flexible gastroscope (Olympus Co, Tokyo, Japan). During each endoscopy, more than 40 pictures were taken by experienced endoscopists blinded to information about the subjects. Gastric mucosal damage was independently graded by using the modified Lanza score (MLS) system by 3 experienced endoscopists blinded to information about subjects[15,16]: grade 0, no erosion and hemorrhage; grade 1, 1–2 erosions and hemorrhages are localized in one area of the stomach; grade 2, 3–5 erosions and hemorrhages are localized in one area of the stomach; grade 3, erosion and hemorrhage are localized in 2 areas of the stomach (total, 6–9 lesions); grade 4, erosion and hemorrhage appear in 3 areas in the stomach or more than 10 lesions in the whole stomach; grade 5, gastric ulcer (Figure 1*A*). Moreover, we graded ulcer/erosion and hemorrhage scores separately. The average of the scores by the 3 experienced endoscopists was used as the MLS for each subject.

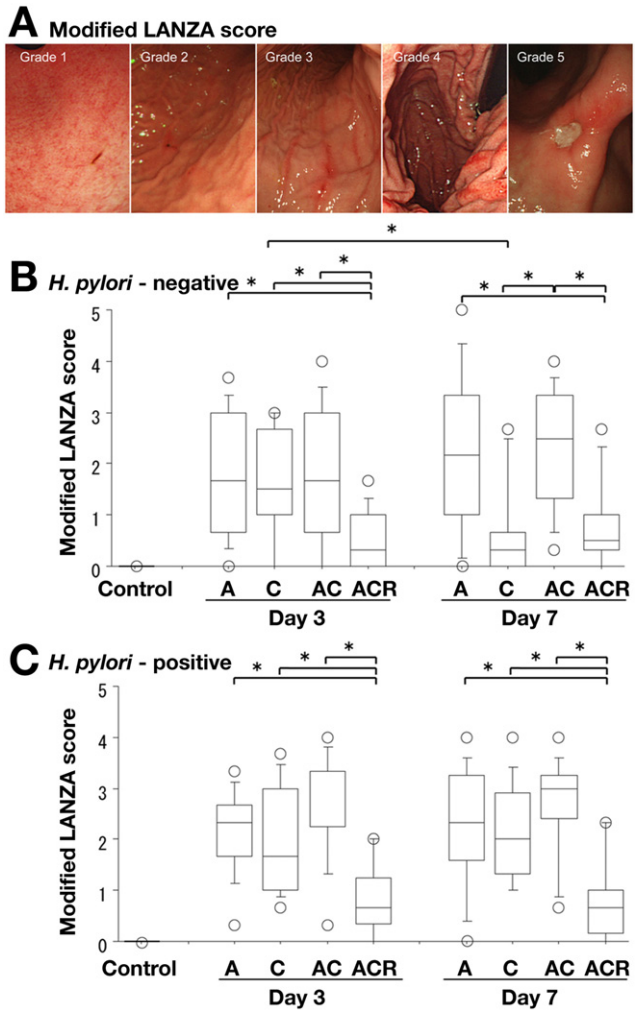

Figure 1. MLS system of gastric mucosal damage on days 3 and 7 in controls and the 4 treatment regimens in *H pylori*–negative (*B*) and –positive subjects (*C*) in study 1. (*A*) Representative endoscopic findings of gastric mucosal injury with different MLSs.[15,16] (*B*) On days 3 and 7, significant gastric mucosal damages were observed with the A, C, and AC regimens in *H pylori*–negative subjects. For the ACR regimen, MLSs on days 3 and 7 were lowest apart from the controls. (*C*) On days 3 and 7, significant gastric mucosal damages were observed with the A, C, and AC regimens in *H pylori*–positive subjects. For the ACR regimen, the MLSs on days 3 and 7 were lowest apart from the controls. *$P < .05$.