ABSTRACT

Background: Current U.S. guidelines recommended thienopyridine (e.g. clopidogrel) for patients who have major gastrointestinal intolerance or complications of aspirin. However, a recent study demonstrated that 12% of patients with a history of ulcer who took clopidogrel had ulcer bleeding within one year. Although proton pump inhibitor (PPI) can prevent recurrent peptic ulcer in clopidogrel users with a history of peptic ulcer, the interaction between PPIs and clopidogrel has drawn much attention recently. Several studies reported that certain PPIs could reduce clopidogrel's antiplatelet effects and increase cardiovascular events. These data suggested that PPIs may potentially inhibit the CYP2C19 pathway and interfere with the conversion of clopidogrel to active form. Therefore, searching for other gastroprotective agents to prevent gastrointestinal events for clopidogrel users is urgently needed in clinical practice.

Aims: To investigate the efficacy of histamine-2 receptor antagonist in the prevention of ulcer recurrence for thienopyridine users.

Methods: 228 thienopyridine (clopidogrel or ticlopidine) users with an ulcer history who do not have gastroduodenal ulcer at initial endoscopy are included. The patients will be randomly assigned to receive either (1) famotidine (40 mg before bedtime) or (2) placebo (before bedtime) for 6 months. Blood sampling for genotyping of CYP2C19 is carried out on enrollment. Platelet aggregation tests are performed in Day 1 and Day 28. Follow-up endoscopy is carried out at the end of the 6th month and whenever severe epigastric pain, hematemesis or melena occurs. Additionally, the episodes of acute coronary syndrome and cerebral vascular accident will be carefully evaluated during the treatment period. Finally, the ulcer recurrence rate, ulcer bleeding rate, incidence of acute
coronary syndrome and cerebral vascular accident between the treatment groups will be compared by chi-square test. Additionally, the independent factors predicting ulcer recurrence will be investigated by multivariate analysis. Furthermore, the effect of CYP2C19 genetic polymorphism on the development of cardiovascular events and platelet aggregation will be analyzed.

INTRODUCTION

Platelet activation and aggregation play an important role in the pathogenesis of arterial thrombosis and lead to ischemic events. Thienopyridine (clopidogrel or ticlopidine) inhibits platelet function by selectively and irreversibly blocking the adenosine diphosphate (ADP) receptor on platelets, thereby affecting ADP-dependent activation of the GpIIb-IIIa complex, the major receptors for fibrinogen present on the platelet surface.\(^1\),\(^2\) Alone or in association with aspirin, clopidogrel is a thienopyridine, which has successfully proved to be beneficial in the treatment of acute coronary syndrome\(^3\) and prevention of ischemic events in patients with atherosclerotic diseases.\(^4\),\(^5\)

The CAPRIE study showed that long-term administration of clopidogrel to patients with atherosclerotic vascular disease is more effective than aspirin in reducing the combined risk of ischemic events.\(^6\) Additionally, Clopidogrel induced fewer episodes of gastrointestinal bleeding than aspirin.\(^6\),\(^7\) The American College of Cardiology-American Heart Association guidelines therefore recommend clopidogrel as an alternative to aspirin for patients with unstable angina or non-ST-segment elevation myocardial infarction who have an aspirin intolerance.\(^8\)

However, a recent study demonstrated that 12% of patients with a history of ulcer who took clopidogrel had ulcer bleeding within one year.\(^9\) Furthermore, the cumulative incidence of recurrent bleeding in clopidogrel users who had ulcer bleeding history (subjects with high gastrointestinal risk) was higher than that in patients who took aspirin plus proton pump inhibitor (PPI).\(^10\) The mechanisms leading to recurrent ulcer bleeding among patients receiving
clopidogrel are unclear. Nonetheless, an animal study revealed that platelet ADP-receptor antagonists impair the healing of gastric ulcers by suppressing the release of platelet-derived growth factors.\textsuperscript{11} We therefore speculate that clopidogrel may also hinder ulcer healing and/or precipitate ulcer formation in humans.

Recently, we have proved that proton pump inhibitor can effectively prevent recurrent peptic ulcers among atherosclerotic patients with a history of peptic ulcer.\textsuperscript{12} However, the interaction of PPIs and clopidogrel has raised the concern for the safety of combination use of the two medicines.\textsuperscript{13-15} Clopidogrel is a prodrug, which must be absorbed in the gastrointestinal tract, and metabolized in the liver to generate active metabolites and acquires its anti-platelet properties. The metabolism of clopidogrel involves CYP2C19 isoenzyme, which is also the key enzyme for the metabolism of most PPIs.\textsuperscript{16} This has led to the assumption that some PPIs may potentially inhibit the CYP2C19 pathway and interfere with the conversion of clopidogrel to active form. Three large retrospective observation studies also reported that patients prescribed clopidogrel who also took PPIs had significant increases in cardiovascular events.\textsuperscript{17-19}

Famotidine is a histamine H2-receptor antagonist that has proved to be well tolerated and able to prevent and heal peptic ulcers in patients receiving conventional NSAIDs.\textsuperscript{20-22} The FAMOUS (Famotidine for the Prevention of Ulcers in Users of Low-dose Aspirin) trial documented that famotidine is effective in the prevention of peptic ulcers and erosive esophagitis in patients taking low-dose aspirin.\textsuperscript{23} However, famotidine is inferior to pantoprazole in preventing recurrence of aspirin-related peptic ulcers or erosions in patients with aspirin-related peptic ulcers/erosions.\textsuperscript{24} The current study is designed to assess the efficacy of histamine-2 receptor antagonist in the prevention of ulcer recurrence for thienopyridine users.

**References**


16. Simon T, Mary-Krause M, Quteineh L, Drouet E, Méneveau N, Steg PG, Ferrières J, Danchin N, Becquemont L; French Registry of Acute ST-Elevation and Non-ST-


PATIENTS AND METHODS

Study population

We will screen for eligible patients who have a past history of gastroduodenal ulcer and underwent endoscopy for dyspeptic symptoms or routine screening, while receiving thienopyridine (either clopidogrel or ticlopidine) therapy to prevent ischemic events. We enroll patients in the study if they meet the following criteria: endoscopic examination reveals normal appearance or pictures of gastritis only; they have received thienopyridine for at least two weeks; they have an atherosclerotic disease such as ischemic heart disease or stroke; they require long-term anti-platelet therapy; and they are adult patients aged $\geq 20$ years. Patients are excluded if they have a history of gastric or duodenal surgery other than oversewing of a perforation; if they are allergic to the study drugs; if they require long-term treatment with non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids, aspirin, or anticoagulant agents; if they are pregnant; if they have active cancer, acute serious medical illness or terminal illness; and if they have gastroesophageal reflux disease.

Study Protocol

Randomization and treatment

Eligible 228 patients are randomly assigned to receive either (1) 40 mg of famotidine (40 mg before bedtime) or (2) placebo (before bedtime) for 6 months. Randomization was carried out with the use of a computer-generated list of random numbers. An independent staff member assigned the treatments according to consecutive numbers that were kept in sealed envelopes. Anticoagulants, cyclooxygense-2 inhibitors, conventional NSAIDs, aspirin, over-the-counter analgesics, corticosteroids, misoprostol, PPIs, sucralfate are prohibited. The administration of an antacid (Iwell, Everest, Taiwan) was permitted for the control of dyspeptic symptoms. Compliance with the regimen are assessed by counting the pills that are returned. If Helicobacter pylori ($H$ pylori) infection is documented on recruitment, a seven-day course of anti-$H$ pylori therapy is administered. Urea breath test is performed at four weeks after the end of anti-$H$ pylori therapy. Patients in whom $H$ pylori infection is not eradicated, as indicated by positive results of urea breath
tests, receive a ten-day course of quadruple therapy consisting of esomeprazole 40 mg b.d., bismuth subcitrate 120 mg q.d.s., tetracycline 500 mg q.d.s., metronidazole 250 mg q.d.s. An additional $^{13}$C urea breath test was conducted to assess the final $H$ pylori status two weeks following the six-month trial for all the patients who have $H$ pylori infection on recruitment. Eradication is defined as a negative result of the final urea breath test.

Blood sampling for genotyping of $CYP2C19$ is carried out on enrollment. Platelet aggregation tests are performed in Day 1 and Day 28. The $CYP2C19$ genotype is determined using the polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) as previous description. Genotypes are classified into three groups: homogeneous extensive metabolizer (homEM; $CYP2C19^*1/CYP2C19^*1$); heterogeneous extensive metabolizer (hetEM; $CYP2C19^*1/CYP2C19^*2$ and $CYP2C19^*1/CYP2C19^*3$); poor metabolizer (PM; $CYP2C19^*2/CYP2C19^*2$, $CYP2C19^*2/CYP2C19^*3$, and $CYP2C19^*3/CYP2C19^*3$).

**Detection of $H$ pylori on recruitment**

On initial endoscopy, a biopsy specimen was obtained from the greater curvature within 5 cm of the pylorus for rapid urease test. A negative CLO test was defined by the absence of a change in color after 24 hours. Additionally, one specimen taken from the greater curvature within 5 cm from the pylorus and another taken from the greater curvature of middle body were subjected to microscopic examination for $H$ pylori with the use of hematoxylin and eosin stain and Warthin-Starry stain if necessary. $H$ pylori was considered to be present if either one of the two tests was positive; it was considered to be absent when both tests were negative.

**Follow-up**

Patients are followed up as outpatients with visits every month. Upper gastrointestinal and cardiovascular symptoms are assessed at each visit. They are asked to return to the outpatient clinic if they have persistent dyspeptic symptoms (epigastric pain, fullness, nausea or vomiting) and to report to the emergency room if they have evidences of gastrointestinal bleeding (hematemesis, melena, or sudden onset of severe epigastric pain), cardiovascular events (chest pain, syncope, or
sudden onset of severe palpitation) or cerebrovascular accidents (conscious disturbance, hemiparesis, or dysphagia). Follow-up endoscopy with biopsy for urease test is performed whenever persistent dyspepsia, severe epigastric pain, hematemesis or melena occurred and at the end of the 6th month. The endoscopists who performed follow-up endoscopy are unaware of the treatment group assignments. The events of acute coronary syndrome and cerebral vascular accidents during the study period are carefully monitored and assessed.

**End points**

The primary end point are the occurrence of gastric and/or duodenal ulcers, as determined by endoscopy, during the 6-month study period. An ulcer is defined as a circumscribed mucosal break at least 0.5 cm in diameter (measured using endoscopy forceps) and with a perceptible depth. Only events that are confirmed by the adjudication committee and that occurred during treatment are included in the analysis. Patients who do not have follow-up endoscopic examination are assumed to have had normal findings. The secondary endpoints are: (1) the occurrence of ulcer or erosion bleeding as defined according to pre-specified criteria – namely, hematemesis or melena documented by the admitting physician, with ulcers or bleeding erosions confirmed on endoscopy, or a decrease in the hemoglobin level of at least 2 g deciliter in the presence of endoscopically documented ulcers or erosions. An erosion is defined as a flat mucosal break of any size; (2) the occurrence of unstable angina defined as rest angina (angina occurring at rest and prolonged more than 20 minutes), new-onset angina (of at least the Canadian Cardiovascular Society Class III severity) and increasing angina (angina occurring more frequently, longer in duration) with ischemic changes in electrocardiogram; (3) acute myocardial infarction defined as at least two positive results of typical chest pain, evolutionary electrocardiogram changes and evolutionary cardiac enzyme changes; (4) the occurrence of ischemic stroke defined as sudden onset of neurological deficit due to cerebral ischemia documented by computed tomography; (5) vascular death defined as death due to cardiovascular diseases or cerebrovascular accidents. Only events that are confirmed by the cardiovascular events review board are included in the analysis.