Point-of-care Measurements of Platelet Inhibition After Clopidogrel Loading in Patients With Acute Coronary Syndrome: Comparison of Generic and Branded Clopidogrel Bisulfate

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ABSTRACT

Purpose: Platelet-function suppression with antiplatelet therapy is effective in preventing and treating cardiovascular disease. Clopidogrel is a thienopyridine derivative that blocks platelet activation by adenosine diphosphate receptor binding. This study demonstrates the effects of generic clopidogrel bisulfate in comparison to branded clopidogrel bisulfate in patients with acute coronary syndromes.

Methods: This prospective, 2-arm, single-center, open-label trial used 1:1 randomization to assign patients to receive generic or branded clopidogrel bisulfate. Patients with unstable angina or non–ST-segment elevation myocardial infarction and scheduled to undergo coronary angiography were enrolled. Platelet function was measured with a $P2Y_{12}$ assay and reported in $P2Y_{12}$ reaction units (PRU) and aspirin reaction units (ARU) after randomization. Platelet function was measured at 2, 4, 8, and 24 hours after 600-mg clopidogrel loading. The clinical outcome was checked at 1 month after coronary angiography.

Findings: Ninety-five patients were enrolled and randomized to the generic or branded group. Ninety patients (62 men [69%], 28 women [31%]; mean age, 58 years) completed the study protocol. The clinical characteristics were similar between the 2 groups. The difference in the baseline PRU measurements between the generic and branded groups was not significant (274.8 [59.7] vs 285.4 [62.4], respectively; $P = 0.414$). There were significant differences in 2-hour PRU (231.1 [71.3] vs 266.9 [67.4]; $P = 0.017$) and 4-hour PRU (227.3 [80.4] vs 265.7 [71.0]; $P = 0.020$); however, 24-hour PRU (200.5 [82.1] vs 220.6 [75.8]; $P = 0.253$) was similar. No death, myocardial infarction, target lesion revascularization, stent thrombosis, or Thrombolysis in Myocardial Infarction–defined major bleeding complications were reported during in-hospital stay or 1-month follow-up.

Implication: In patients with ACS, loading of generic clopidogrel bisulfate was associated with an antiplatelet effect comparable to that of branded clopidogrel bisulfate. ClinicalTrials.gov identifier: NCT02060786. (*Clin Ther.* 2014;36:1588–1594)
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Key words: acute coronary syndrome, antiplatelet, clopidogrel.

INTRODUCTION

Platelets have an important role in cardiovascular events such as ischemic heart disease and stroke. Platelet-function suppression with antiplatelet therapy is effective in preventing and treating cardiovascular disease. Clopidogrel is a thienopyridine derivative that blocks the activation of platelets by binding the adenosine diphosphate receptor. Dual antiplatelet

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therapy with aspirin and clopidogrel is well known in clinical practice for reducing the risk for cardiovascular events in patients with acute coronary syndromes (ACS).[1–4] Because the drug-eluting stent delays endothelization in the coronary artery, early interruption of antiplatelet therapy increases the risk for stent thrombosis.[5] Almost all clinical guidelines recommend at least 1 year of dual antiplatelet therapy after drug-eluting stent implantation.[6,7] In patients at high risk for cardiovascular disease, the duration of dual antiplatelet therapy can be prolonged to >1 year. The application of generic clopidogrel bisulfate could be a cost-effective treatment option. After the bioequivalence of a generic formulation of clopidogrel bisulfate and branded clopidogrel bisulfate was studied, the generic formulation was approved for use by the Korea Food and Drug Administration in 2006 and can be regularly prescribed by physicians. In a clinical, randomized, pharmacodynamics comparison study in healthy subjects, there was no significant difference in the percentage of inhibition between the 2 groups. In the Accel-Generic study,[8,9] after 6 months of stenting, the branded formulation was replaced with the generic as antiplatelet therapy. Platelet-function measurements showed comparable inhibition of adenosine diphosphate–induced platelet aggregation.

In patients with ACS, antiplatelet therapy with a 600-mg loading dose of clopidogrel is important in preventing major cardiovascular adverse events after percutaneous coronary intervention (PCI).[10,11] The maximal platelet aggregation inhibition effect has been reported to have been obtained at 2 hours after loading of clopidogrel.[12,13]

In this study, we demonstrate the effects of generic clopidogrel bisulfate in comparison to branded clopidogrel bisulfate in the treatment of patients with ACS in whom PCI was planned. Until now, there has been no known study of antiplatelet effects in patients with ACS after either treatment with generic or branded clopidogrel.

PATIENTS AND METHODS

Inclusion Criteria

Patients with unstable angina or non–ST-segment elevation myocardial infarction (NSTEMI) were enrolled. Patients were eligible if coronary angiography was planned and they were aged ≥18 and ≤75 years.

Exclusion Criteria

Patients with recent treatment with clopidogrel, cilostazol, glycoprotein IIb/IIIa antagonist, and/or anticoagulation therapy (heparin, warfarin), active bleeding (peptic ulcer, trauma or intracranial hemorrhage), allergy to antiplatelet agents, bleeding diathesis (blood coagulation disorders, uncontrolled severe hypertension, history of severe bleeding), history of drug or alcohol abuse, STEMI, pregnancy, low platelet count (<100,000 /L), abnormal prothrombin time or partial thromboplastin time, liver disease (bilirubin >2 mg/dL, alanine or aspartate aminotransferase >100 IU), renal failure (creatinine >2.0 mg/dL), malignancy, and/or current treatment with a proton pump inhibitor, NSAID, or statin (except atorvastatin) were excluded. Each patient provided written informed consent to participate in the study. The study protocol was approved by the Ajou University Hospital institutional review board.

Study Design

This prospective, 2-arm, single-center, open-label trial used 1:1 randomization to assign patients to receive generic* or branded† clopidogrel bisulfate and was conducted at the Ajou University Hospital, Ajou University School of Medicine, Suwon, Republic of Korea. After randomization, baseline platelet function was measured with the VerifyNow point-of-care $P2Y_{12}$ assay (Accumetrics, San Diego, California). Platelet function was measured at 2, 4, 8, and 24 hours after loading of clopidogrel 600 mg. Coronary angiography and PCI were performed using conventional methods. After a drug-eluting stent was inserted into the coronary artery, clopidogrel 75 mg once daily for 30 days was prescribed. Clinical outcome was checked at 30 days (Figure 1).

Platelet-Function Measurement

A platelet-reactivity test was performed with the VerifyNow assay. The results are reported as $P2Y_{12}$ reaction units (PRU) and aspirin reaction units (ARU).

End Points

The primary end point was the PRU level measured at 2 hours after clopidogrel loading. Secondary end

*Trademark: Plavitor® (Dong-A Pharmaceutical Corporation, Seoul, Korea).

†Trademark: Plavix® (Bristol-Myers Squibb Company [New York, New York] and The sanofi-aventis Group [Bridgewater, New Jersey]).

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