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Original article

Clinical significance of platelet reactivity during prasugrel therapy in patients with acute myocardial infarction

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ABSTRACT

Background: Although some studies have examined platelet reactivity (PR) during prasugrel treatment, little is known about PR during the early treatment period and its clinical significance in Japan.
Methods: We investigated the early and medium-term efficacy and safety of prasugrel in patients with acute myocardial infarction (AMI) undergoing primary percutaneous coronary intervention (PCI). Seventy-eight patients were enrolled and PR was measured (in $P2Y_{12}$ reaction units; PRU) by the VerifyNow $P2Y_{12}$ assay (Accumetrics, San Diego, CA, USA).
Results: In 44 patients, serial measurement revealed that PR was significantly higher at 2 h after administration of the 20-mg loading dose of prasugrel than on the morning of the second day at 17.6 ± 6.6 h after administration (191.6 ± 75.5 vs. 138.5 ± 68.9 PRU). During the 8-month follow-up period, bleeding events occurred in 18 patients (23.1%) (GUSTO minor: 15 patients). Multivariate regression analysis identified oral anticoagulant use as a significant predictor of bleeding events during admission [odds ratio (OR): 4.214, 95% confidence interval (CI): 1.005–17.669, $p = 0.049$]. Administration of prasugrel via a nasogastric tube was a significant predictor of high on-treatment platelet reactivity (HTPR) (PRU ≥ 230) (OR: 43.100, 95% CI: 4.517–411.251, $p = 0.001$). In addition, HTPR was a significant predictor of major adverse cardiac events (cardiovascular death, non-fatal myocardial infarction, stent thrombosis, stroke, and sustained ventricular tachycardia) during the 8-month follow-up period (OR: 4.911, 95% CI: 1.164–20.722, $p = 0.030$).
Conclusions: It is feasible to treat AMI patients with prasugrel. HTPR is a significant independent risk factor for adverse events in AMI patients receiving prasugrel after primary PCI.

Introduction

Dual antiplatelet therapy with aspirin and a thienopyridine $P2Y_{12}$ receptor inhibitor, such as clopidogrel or prasugrel, plays a crucial role in the management of patients with acute myocardial infarction (AMI) undergoing percutaneous coronary intervention (PCI). However, clopidogrel has a slow onset of action, and it has been suggested that its pharmacologic effects can be insufficient to adequately suppress platelet aggregation and prevent thrombotic events due to individual variability [1–3]. Prasugrel is a novel thienopyridine antiplatelet agent that induces more rapid, potent, and consistent inhibition of platelet activity than clopidogrel [4]. Therefore, use of prasugrel might help to reduce both ischemic events and bleeding events in AMI patients.

Measurement of platelet reactivity is considered to be important because the risk of thrombotic events was reported to be increased in patients with high on-treatment platelet reactivity (HTPR), which indicates a poor response to antiplatelet agents [5–7], while the risk of bleeding is increased in patients with low on-treatment platelet reactivity, which indicates a strong response to these drugs [8,9]. However, few studies have examined the relationships between high/low platelet reactivity and clinical events in patients receiving prasugrel, especially during the acute phase of treatment or at medium-term follow-up. Therefore, we attempted to clarify the clinical significance of platelet reactivity during prasugrel therapy in Japanese AMI patients undergoing PCI.

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Materials and methods

Patients

Seventy-eight AMI patients who underwent primary PCI between July 2014 and November 2015 were studied. All of the patients were assessed during admission and then were followed for 8 months after PCI. AMI was diagnosed on the basis of chest pain persisting for >30 min, a >3-fold increase of serum creatine kinase and/or ST segment elevation >2 mm in two adjacent leads on the electrocardiogram (ECG). Cardiogenic shock was defined as the presence of hypotension (systolic blood pressure <90 mmHg) and evidence of vital organ hypoperfusion (cool extremities, oliguria, and clouded sensorium). Stroke was defined as the presence of neurological symptoms or signs consistent with stroke and confirmation by magnetic resonance imaging. Primary PCI was performed in patients who presented <12 h after the onset of chest pain or other symptoms according to the recommendations for PCI in patients with AMI [10,11]. The loading dose of prasugrel (20 mg) was administered as soon as possible in the coronary care unit or cardiac catheter laboratory, and then a maintenance dose of 3.75 mg was administered once daily in the morning. All of the patients were also treated with aspirin (a 200-mg loading dose administered in the coronary care unit before PCI and 100 mg/day for maintenance) and dual antiplatelet therapy was continued for 12 months.

Pharmacodynamic analysis

Residual platelet reactivity was assessed by using the VerifyNow $P2Y_{12}$ assay (Accumetrics, San Diego, CA, USA) at 2 h after administration of the loading dose of prasugrel and on the morning of the second day before the first maintenance dose. This assay measures adenosine diphosphate-induced platelet aggregation from the increase in light transmittance and the results are reported in $P2Y_{12}$ reaction units (PRU) [12]. In the present study, HTPR was defined as a PR value ≥230 PRU [13].

Safety

Bleeding events were recorded from the start of prasugrel administration to the end of the 8-month follow-up period. Events were classified into 5 types according to the bleeding academic research consortium (BARC) criteria [14] and were categorized from mild to severe or life-threatening according to the global utilization of streptokinase and tissue plasminogen activator for occluded coronary arteries (GUSTO) criteria [15].

Efficacy and endpoint

Major adverse cardiac events (MACE) were defined as cardiovascular death, non-fatal myocardial infarction, stent thrombosis, stroke, or sustained ventricular tachycardia occurring from admission to 8-month follow-up. The primary endpoint was the frequency of MACE at 8-month follow-up. We carefully collected data on clinically relevant events. The type and frequency of ventricular arrhythmias were evaluated from ECGs recorded in the catheter laboratory, coronary care unit, or ward. Sustained arrhythmias were defined as those that continued for >30 s.

Statistical analysis

Results are shown as the mean ± standard deviation and were analyzed by using the paired Student *t*-test and Pearson's chi-square test. Values of $p < 0.05$ were considered to indicate statistical significance. Univariate and multivariate regression analyses were performed to evaluate the independent contributions of bleeding events and clinical characteristics to HTPR. Odds ratios (OR) and 95% confidence intervals (CI) were also calculated. All statistical analyses were performed on a personal computer with the SPSS for Windows statistical package (SPSS Inc., Chicago, IL, USA).

Results

Clinical and lesional characteristics

The baseline clinical and lesional characteristics of the subjects are shown in Table 1. The mean age of the patients was 64.8 ± 13.0 years, and mean body weight was 63.2 ± 13.5 kg. Five patients (6.4%) had chronic kidney disease (CKD) with an estimated glomerular filtration rate (eGFR) <30 ml/min/1.73 m^2. Prasugrel was administered via a nasogastric tube in 8 patients (10.3%). The transradial approach was used for PCI in 22 patients (28%). Eleven patients (14.1%) also received oral anticoagulants (OAC), including warfarin in 10 patients and a novel OAC in 1 patient. Twelve patients (15.4%) had cardiogenic shock.

Residual platelet reactivity

In 44 patients, serial measurement revealed that residual platelet reactivity was significantly higher at 2 h after the loading dose of prasugrel than in the morning on day 2 after a mean of 17.6 ± 6.6 h (191.6 ± 75.5 vs. 138.5 ± 68.9 PRU, respectively; $p < 0.001$) (Fig. 1). However, platelet reactivity at 2 h after the loading dose was below the threshold for HTPR. Also, platelet reactivity on day 2 showed no significant difference between the 44 patients with serial measurement and the other 34 patients who were only tested on day 2 (138.5 ± 68.9 vs. 148.9 ± 66.5 PRU, $p = 0.679$) (data not shown in figure).

Safety

The incidence of bleeding events was 23.1% (18/78) during the 8-month follow-up period. Fifteen of the 18 events noted during follow-up were type 1 or 2 according to the BARC classification and were minor events according to the GUSTO classification. The details of the bleeding events were as follows: PCI puncture site bleeding: 9, epistaxis: 3, fatal cerebral hemorrhage after infarction on admission: 1, bleeding gastric ulcer: 1, melena: 2, gingival bleeding: 1, Mallory-Weiss syndrome: 1. The timing of bleeding events is shown in Fig. 2, revealing that many events occurred in

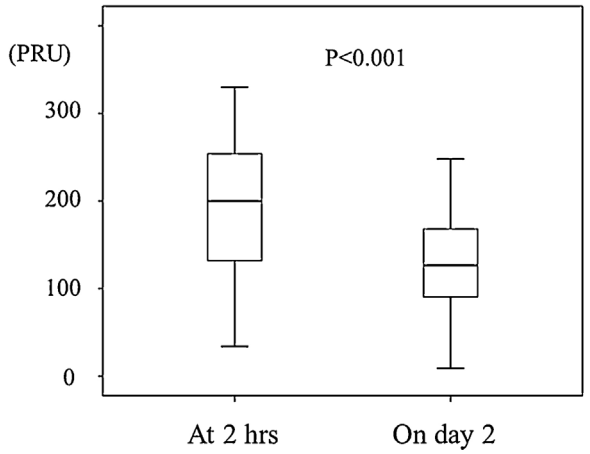

Fig. 1. Platelet reactivity at 2 h after administration of the prasugrel loading dose and on day 2. At both times, platelet reactivity was below the threshold for high on-treatment reactivity. PRU, $P2Y_{12}$ reaction units.

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