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Original article

Impact of concomitant use of proton-pump inhibitors and thienopyridine derivatives on the antiplatelet effects

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Platelet inhibitors;
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Summary
Background: Although there has been an intense debate whether concomitant use of proton-pump inhibitors (PPIs) attenuates the antiplatelet effects of thienopyridine derivatives, the drug—drug interaction remains unclear in Japanese patients with coronary artery disease.
Methods and results: Platelet function test was performed in 461 patients who were scheduled for or had undergone stent implantation, treated with 100 mg/day of aspirin and a thienopyridine (200 mg/day of ticlopidine or 75 mg/day of clopidogrel) for at least 14 days. Adenosine diphosphate-induced platelet aggregation was evaluated with screen filtration pressure method, and the upper quartile of high platelet reactivity was defined as high on-treatment platelet reactivity (HPR). PPI use was at physician's discretion. Patients taking a thienopyridine plus a PPI ($n = 166$) were older and had a higher incidence of acute coronary syndromes on admission compared with patients taking a thienopyridine without a PPI ($n = 295$). The rate of HPR was higher in patients taking a thienopyridine plus a PPI than in patients taking a thienopyridine without a PPI (31% vs 21%, $p = 0.01$). On multivariate logistic regression analysis, independent predictors of HPR were concomitant PPI use [odds ratio (OR): 1.66, 95% confidence interval (CI): 1.03—2.68], diabetes mellitus (OR: 1.76, CI: 1.11—2.81), and calcium channel blockers use (OR: 1.93, CI: 1.18—3.18). However, there was no significant difference in the rate of extremely high platelet reactivity [58 patients (12.5%) with PATI < 4.0 μM] between patients treated with a thienopyridine plus a PPI and those without a PPI (14% vs 11%, NS).

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Conclusion: HPR was frequently observed in Japanese patients treated with thienopyridines plus PPIs compared to those without PPIs. Further prospective studies are needed to estimate the risk of adverse cardiovascular events associated with concomitant use of PPIs and thienopyridines.

Introduction

Thienopyridine derivatives in addition to aspirin have become a cornerstone of medical treatment for patients who have acute coronary syndromes (ACS) and/or receive stent implantation [1—3]. Both ticlopidine and clopidogrel are prodrugs which must be metabolized by the cytochrome P (CYP) 450 enzyme system to generate their active metabolites [4]. Individual variability in the response of platelets to thienopyridine derivative treatment might be partially related to the level of activation of the CYP450.

Although a prescription of a proton-pump inhibitor (PPI) is recommended to minimize the risk of gastrointestinal bleeding complications in all patients receiving dual antiplatelet therapy [5], several studies showed that PPIs attenuated the antiplatelet effects [6—9] and clinical efficacy of clopidogrel [10,11]. These concerns are attributed to the competitive inhibition of CYP2C19 by PPIs, which is involved in the metabolic activation of clopidogrel. Moreover, a reduced function of CYP2C19 is associated with a reduced response to clopidogrel and increased risk of adverse cardiovascular events [12—16]. By contrast, recent studies showed no increase in the risk of cardiovascular events in patients taking clopidogrel plus PPIs [17—19]. With these conflicting data, the clopidogrel—PPIs interaction remains unclear. We retrospectively assessed the impact of concomitant use of PPIs on platelet reactivity in patients who were scheduled for or had undergone elective stent implantation and had received chronic dual antiplatelet therapy.

Methods

Patients

Between June 2006 and December 2009, platelet function test was performed in 461 patients with coronary artery disease (363 men; mean age, 68 years), who were scheduled for or had undergone stent implantation. All study patients were on chronic dual antiplatelet therapy with 100 mg/day of aspirin and a Japanese standard dose of thienopyridine derivatives (200 mg/day of ticlopidine or 75 mg/day of clopidogrel) for at least 14 days. Thienopyridines and antacids were prescribed at each doctor's discretion. We excluded patients with oral anticoagulant agents, or a baseline hemoglobin level of <8 g/dl or a platelet count of <100,000/mm^3. The study protocol was approved by the ethics committee of Yokohama City University. Written comprehensive informed consent was obtained from all patients.

Laboratory analyses

In the early morning, peripheral venous blood samples were drawn using a 21G needle and added to a test tube containing a final concentration of 0.313% sodium citrate. Whole blood samples were kept at room temperature for 1 h, and thereafter platelet aggregation activity in response to adenosine diphosphate was measured by the screen filtration pressure method with WBA-neo® (ISK, Tokyo, Japan). Aggregation reactions were started by adding 4 or 5 different concentrations of adenosine diphosphate (2, 4, 8, 16, and 32 μM if needed) to whole blood in test tubes, while constantly stirring at 37 °C. Five minutes after stimulation, the absorbing pressure was measured through a micro-sieve with 30 μm × 30 μm holes. The estimated adenosine diphosphate concentration resulting in 50% filter blockage by platelet aggregation was calculated and defined as the platelet aggregation threshold index (PATI) [20,21]. Unfortunately, there is no consensus on the definition of high on-treatment platelet reactivity (HPR) derived by this method. Because thienopyridine responsiveness is normally distributed [22], and HPR was defined as the upper quartile of high platelet reactivity in some previous studies [23—26], the first quartile was defined as HPR in the present study.

Renal insufficiency was defined as an estimated glomerular filtration rate of <60 mL/min/1.73 m^2. Anemia was defined as a baseline hemoglobin level of <13 g/dl in men and <12 g/dl in women.

Statistical analysis

Categorical variables were reported as percentages and compared by the chi-square test. Continuous variables were reported as means ± SD or median (interquartile range) and compared by Student's *t*-test. Potential predictors with *p*-values of <0.20 on univariate analysis which were demographic, clinical, and medicinal variables were included in multivariate logistic regression analysis. Odds ratios (OR) and 95% confidence intervals (CI) were calculated. *p*-Values of <0.05 were considered to indicate statistical significance. Data were analyzed with SPSS 17 (SPSS, Inc., Chicago, IL, USA).

Results

Patient characteristics

Patients taking a thienopyridine plus a PPI ($n = 166$) were older (69 ± 9 vs 67 ± 10 years, $p = 0.01$) and had a lower incidence of hypertension (62% vs 74%, $p < 0.01$), and had a higher incidence of ACS on admission (23% vs 13%, $p < 0.01$), prior coronary artery bypass graft surgery (11% vs 5%, $p = 0.01$), anemia (52% vs 43%, $p < 0.01$), and previous gastroduodenal ulcer (14% vs 4%, $p < 0.01$) compared with patients taking a thienopyridine without a PPI ($n = 295$). There were no significant differences in the other baseline characteristics between the 2 groups (Table 1A) Among patients treated with clopidogrel, higher percentage of ACS on admission and lower percentage of hypertension were observed in PPI users than in non-PPI users. Among patients treated