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Comparison of Omeprazole and Pantoprazole Influence on a High 150-mg Clopidogrel Maintenance Dose

The PACA (Proton Pump Inhibitors And Clopidogrel Association) Prospective Randomized Study

Thomas Cuisset, MD,*†‡ Corinne Frere, MD,†‡ Jacques Quilici, MD,* Raphael Poyet, MD,* Bénédicte Gaborit, MD,†‡ Laurent Bali, MD,* Olivier Brissy, MD,* Pierre-Emmanuel Morange, MD, PHD,†‡ Marie-Christine Alessi, MD, PHD,†‡ Jean-Louis Bonnet, MD*

Marseille, France

Objectives This study sought to compare the effect of 2 proton pump inhibitors (PPIs) on platelet response to clopidogrel after coronary stenting for non–ST-segment elevation acute coronary syndrome (NSTE ACS).

Background Use of omeprazole has been reported to significantly decrease the clopidogrel antiplatelet effect because of cytochrome P450 interaction. Because all PPIs are metabolized by CYP2C19, but to a varying degree, we hypothesized that the reported negative omeprazole–clopidogrel drug interaction may not be caused by a class effect.

Methods A total of 104 patients undergoing coronary stenting for NSTE ACS were prospectively included and randomized to omeprazole or pantoprazole 20 mg. They received at discharge 75-mg aspirin and 150-mg clopidogrel. Platelet reactivity index (PRI) vasoactive stimulated phosphoprotein (VASP) was used to assess clopidogrel response and adenosine diphosphate (ADP)–induced aggregation for platelet reactivity (ADP-Ag).

Results After 1 month, patients receiving pantoprazole had a significantly better platelet response to clopidogrel as assessed with the PRI VASP: 36 ± 20% versus 48 ± 17% ($p = 0.007$). We identified more clopidogrel nonresponders in the omeprazole group than in the pantoprazole group: 44% versus 23% ($p = 0.04$), odds ratio: 2.6 (95% confidence interval: 1.2 to 6.2). Conversely, we did not observe any significant difference in platelet reactivity with ADP-Ag between the omeprazole and pantoprazole groups: 52 ± 15% and 50 ± 18%, respectively ($p = 0.29$).

Conclusions The present findings suggest the preferential use of pantoprazole compared with omeprazole in patients receiving clopidogrel to avoid any potential negative interaction with CYP2C19. (J Am Coll Cardiol 2009;54: 1149–53) © 2009 by the American College of Cardiology Foundation

Several studies have shown a broad variability of biological response to clopidogrel and its clinical relevance (1–4). Mechanisms underlying this variability of response remain controversial and multiple factors are involved, including metabolic factors and genetic factors (4). Clopidogrel is a prodrug, which must be metabolized in the liver to generate an active metabolite and acquire its antiplatelet properties (5). Accordingly, clopidogrel response has been related to the level of activation of the CYP450 (6). Moreover, the loss-of-function allele of CYP2C19 has been associated with a poor response to clopidogrel in both healthy volunteers and patients (7–9), and with worse clinical outcomes in clopidogrel-treated patients (10–12). In addition, medications metabolized by CYP450, such as omeprazole or atorvastatin, have been shown to influence clopidogrel effect (13,14). Omeprazole has been associated with a lower efficacy of clopidogrel as assessed by the platelet reactivity index vasoactive stimulated phosphoprotein (PRI VASP) (13). Conversely, new proton pump inhibitors (PPIs) such as pantoprazole or esomeprazole have shown no effect on biological response to clopidogrel (15). Because many PPIs are metabolized by CYP2C19, but to a varying degree, the

From the *Département de Cardiologie and †Laboratoire d'Hématologie, CHU Timone, Marseille, France; and ‡INSERM, UMR 626, Faculté de Médecine, Marseille, France. Supported by grants from the Assistance Publique Hôpitaux de Marseille.

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Abbreviations and Acronyms

ADP = adenosine diphosphate

ADP-Ag = adenosine diphosphate-induced aggregation for platelet reactivity

MFI = median fluorescence intensity

NSTE ACS = non–ST-segment elevation acute coronary syndrome

PPI = proton pump inhibitor

PRI = platelet reactivity index

VASP = vasoactive stimulated phosphoprotein

reported negative omeprazole–clopidogrel drug interaction may not be caused by a class effect. We therefore designed a prospective, randomized study to compare the influence of omeprazole and pantoprazole on the antiplatelet effect of a high 150-mg maintenance dose of clopidogrel in patients undergoing coronary stenting for non–ST-segment elevation acute coronary syndrome (NSTE ACS).

Methods

Study protocol. Consecutive patients admitted for NSTE ACS in our institution were eligible for this prospective study if they had undergone successful coronary stenting. We defined NSTE ACS as clinical symptoms compatible with acute myocardial ischemia within 12 h before admission and at least 1 of the following: a new finding of ST-segment changes in at least 2 leads, elevated levels of cardiac markers, or coronary artery disease as documented by a history of revascularization or myocardial infarction.

The exclusion criteria were a history of bleeding diathesis, persistent ST-segment elevation ACS, New York Heart Association functional class IV, percutaneous intervention or coronary artery bypass grafting <3 months, contraindications to antiplatelet therapy, platelet count <100 g/l, creatinine clearance <25 ml/min, use of glycoprotein IIb/IIIa antagonist before the procedure, and prior use of PPI or clopidogrel. The design of the study is described in Figure 1. Patients received oral loading doses of 250-mg aspirin and 600-mg clopidogrel at least 12 h before stenting. Initial platelet parameters were assessed between 12 and 24 h after the loading dose (T0). Anticoagulation was obtained with low-weight molecular heparin (enoxaparin) when possible, or unfractionated heparin in patients older than 75 years of age, or with renal failure. Use of a glycoprotein IIb/IIIa antagonist was allowed at the operator's discretion during the procedure. Afterward, patients were discharged with the following dual antiplatelet therapy: 75-mg aspirin and 150-mg clopidogrel daily. Patients were randomized 1:1 to omeprazole 20-mg or pantoprazole 20-mg with randomization by sealed envelopes. Platelet tests were performed 1 month after hospital discharge at clinical follow-up (T1). The study protocol was approved by the ethics committee of our institution, and patients gave written informed consent for participation.

Blood samples and platelet parameters. Blood samples for testing platelet reactivity were drawn at least 12 h after the loading dose of aspirin and clopidogrel, and before administration of glycoprotein IIb/IIIa antagonist if needed. The blood–citrate mixture was centrifuged at 120 *g* for 5 min. The resulting platelet-rich plasma was kept at room temperature for use within 1 h. The platelet count was determined in the platelet-rich plasma sample and adjusted to 2.5×10^8 ml^{-1} with homologous platelet-poor plasma. Platelets were stimulated with adenosine diphosphate (ADP) (10 μmol/l), and aggregation was assessed with a PAP4 Aggregometer (Biodata Corporation, Wellcome, Paris, France). Aggregation was expressed as the percentage change in light transmittance from baseline with platelet-poor plasma as a reference. Here we report data on maximal

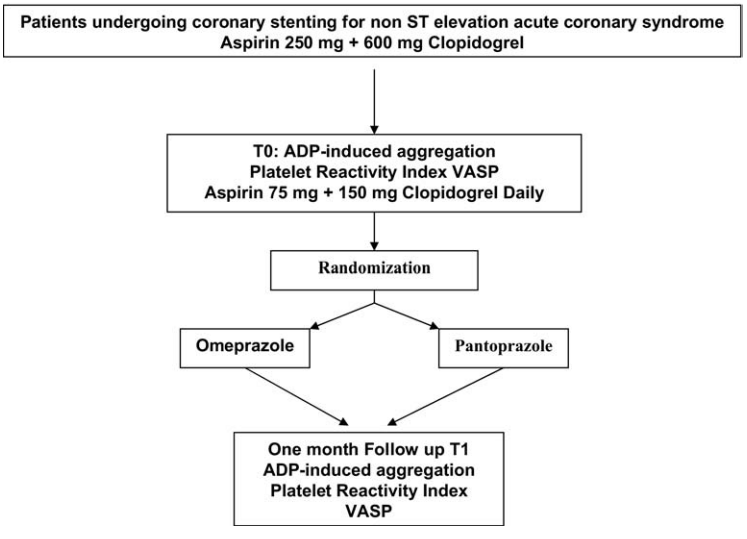

Figure 1 Design of the Study

ADP = adenosine diphosphate; T0 = baseline level; VASP = vasoactive stimulated phosphoprotein.

intensity of ADP-induced platelet aggregation (ADP-Ag). The coefficient of variation of maximal intensity of platelet aggregation with ADP was measured at 6.5%. An ADP-Ag >70% was defined as high post-treatment platelet reactivity as previously described (3,4,8).

To determine the VASP phosphorylation state of whole blood, we used a standardized flow cytometric assay (Platelet VASP, Diagnostica Stago [Biocytex], Asnières, France), which is an adaptation of the method of Schwarz et al. (16). Briefly, a citrated blood sample was incubated with PGE1 or with PGE1 and ADP 10 μmol/l for 10 min and fixed with paraformaldehyde, after which the platelets were permeabilized with nonionic detergent. Analyses were performed on an EPICS XL-MCL flow cytometer (Beckman Coultronics, Margency, France), the platelet population was identified from its forward and side scatter distribution, and 10,000 platelets were gated. A PRI VASP was calculated from the median fluorescence intensity (MFI) of samples incubated with PGE1 or PGE1 and ADP according to the formula: PRI VASP = $[(MFI_{(PGE1)} - MFI_{(PGE1+ADP)})/MFI_{PGE1}] \times 100$. Clopidogrel nonresponse was defined as PRI VASP >50%.

End points. The primary end point of the study was clopidogrel response 1 month after hospital discharge assessed with the specific method, PRI VASP. The secondary end point was post-treatment platelet reactivity assessed with ADP-Ag.

Statistical analysis. Statistical analysis was performed using the Graphpad Prism Software (version 4.00, Graphpad Software, Inc., San Diego, California). We estimated that a study sample size of 100 patients would enable a one-half standard deviation difference (10% difference in PRI VASP between both groups) to be detected, with an 80% statistical power and a 5% alpha risk. Continuous variables are expressed as mean ± SD. Categorical variables are expressed as frequencies and percentages. Comparisons between groups were made with the chi-square or Fisher exact test for categorical variables and nonparametric statistical testing (Mann-Whitney) for continuous variables. Values of $p < 0.05$ were considered statistically significant.

Results

A total of 104 consecutive patients were prospectively included and randomized to omeprazole (n = 52) or pantoprazole (n = 52). Baseline characteristics of the patients are summarized in Table 1. Baseline levels of ADP-Ag and PRI VASP (T0) were not significantly different between patients randomized to omeprazole or pantoprazole: 39.5 ± 19% versus 39.8 ± 19% (p = 0.84) and 35 ± 21% versus 30 ± 21% (p = 0.36), respectively.

At 1-month follow-up, in the whole population, mean PRI VASP and ADP-Ag were 41 ± 19% and 51 ± 17%, respectively. The PRI VASP and ADP-Ag significantly correlated (r = 0.55, p < 0.01). The prevalence of clopidogrel nonresponders was 34% (n = 35) with PRI VASP, and the rate of high post-treatment platelet reactivity was 12% (n = 12).

Table 1 Baseline Characteristics of the Patients

Characteristics	Omeprazole (n = 52)	Pantoprazole (n = 52)	p Value
Male	47 (90)	43 (82)	0.25
Age (yrs)	64.5 ± 12	62.5 ± 13	0.34
Body mass index (kg/m^2)	26.4 ± 4	26.1 ± 5	0.30
Cardiovascular risk factors			
Hypertension	34 (65)	22 (42)	0.02
Diabetes mellitus	11 (21)	11 (21)	1.00
Smoker	21 (40)	24 (46)	0.55
Dyslipidemia	28 (53)	28 (54)	1.00
Familial history	17 (33)	11 (21)	0.19
Discharge medications			
Statins	36 (69)	40 (77)	0.78
Beta-blocker	37 (71)	44 (84)	0.10
Calcium-channel blockers	10 (19)	8 (15)	0.60
Ejection fraction	10 (19)	8 (15)	0.60
Biological data			
Creatinine (mg/dl)	96 ± 11	100 ± 17	0.67
CRP (mmol/l)	2.4 ± 0.8	2.7 ± 0.5	0.68
Platelet count	214 ± 33	227 ± 45	0.60
ADP-Ag T0 (%)	39.5 ± 19	39.8 ± 19	0.84
PRI VASP T0 (%)	35 ± 21	30 ± 21	0.36
Procedural data			
Glycoprotein IIb/IIIa antagonists	23 (44)	28 (54)	0.37
Drug-eluting stent	18 (35)	17 (33)	0.78

Values are mean ± SD for quantitative variables and n (%) for qualitative variables.
ADP-Ag = adenosine diphosphate-induced aggregation for platelet reactivity; CRP = C-reactive protein; PRI VASP = platelet reactivity index vasoactive stimulated phosphoprotein; T0 = baseline level.

After 1 month of PPI treatment (T1), patients receiving pantoprazole had a significantly better platelet response to clopidogrel as assessed with the PRI VASP: 36 ± 20% versus 48 ± 17% (p = 0.007) (Fig. 2A). The differences of PRI VASP between the 2 measures were significantly different with pantoprazole and omeprazole: 3.6 ± 15% versus 11.2 ± 16%, respectively (p = 0.03). We identified more clopidogrel nonresponders in the omeprazole group than in the pantoprazole group: 44% versus 23%, p = 0.04, odds ratio: 2.6 (95% confidence interval: 1.2 to 6.2) (Fig. 3).

We did not observe any significant difference for platelet reactivity with ADP-Ag between the omeprazole and pantoprazole groups: 52 ± 15% and 50 ± 18%, respectively (p = 0.29) (Fig. 2B).

Discussion

The present study suggests that the degree of the interaction between clopidogrel and PPI is not homogeneous within the class of PPIs and is less marked with pantoprazole than with omeprazole. It confirms that the use of omeprazole significantly reduced the antiplatelet activity of clopidogrel, even with a high maintenance dose of clopidogrel, and that other PPIs, such as pantoprazole, must be preferred in clopidogrel-treated patients. Interestingly, the PPI had no

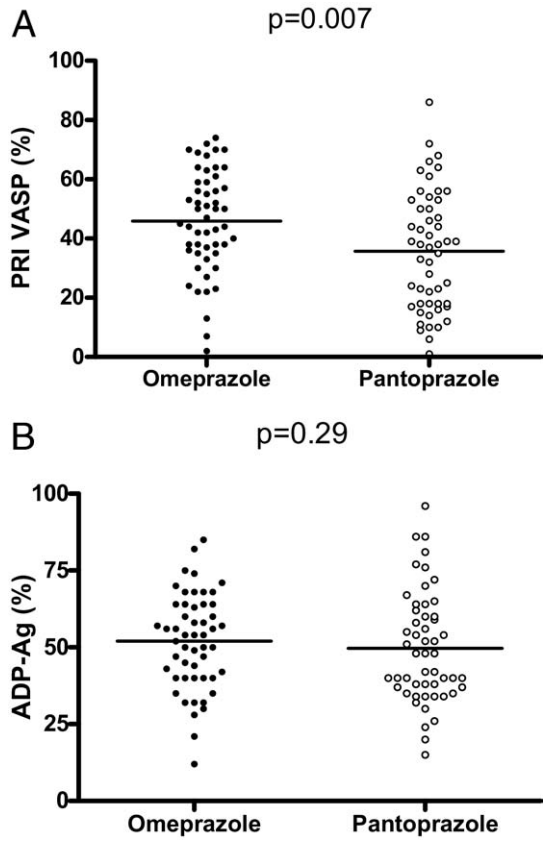

Figure 2 Platelet Parameters and According to Proton Pump Inhibitors

Clopidogrel response with platelet reactivity index vasoactive stimulated phosphoprotein (PRI VASP) **(A)** and platelet reactivity with adenosine diphosphate–induced platelet aggregation (ADP-Ag) **(B)** according to proton pump inhibitor treatment.

significant effect on platelet reactivity assessed with ADP-Ag, whereas omeprazole significantly blunted the decrease in PRI VASP with clopidogrel. This finding underlined the divergence between the 2 tests: ADP-Ag, despite the use of ADP stimulation, may reflect other platelet pathways, whereas levels of VASP phosphorylation/dephosphorylation accurately reflect P2Y12 inhibition/activation (16). Biological studies have shown a broad interindividual variability of platelet response to clopidogrel, and more recently, a low response to clopidogrel has been associated with an increased risk of ischemic events (1–4) and is now a growing concern in the medical community. Several mechanisms have been proposed to explain this variability of response, including genetic factors, metabolic parameters, or interaction with other medications (1).

The active metabolite of clopidogrel, which irreversibly blocks platelet ADP P2Y12 receptors, arises from complex biochemical reactions involving several CYP450 isoforms (5). Lau et al. (6) reported that CYP3A4 metabolic activity correlated with between-subject variability in clopidogrel response. The CYP450 isoform 2C19 plays a major role in this metabolism, and its activity dramatically influences the antiplatelet effect of clopidogrel. This effect has been highlighted recently with the loss-of-function CYP2C19*2 allele, associated with a low response to clopidogrel and worse clinical outcome (7–12). Several medications are also metabolized by CYP450, suggesting potential drugs–clopidogrel interactions. Accordingly, interaction between atorvastatin or omeprazole and clopidogrel has been suggested in biological studies (13,14). Gilard et al. (13) showed a significant interaction between omeprazole and clopidogrel with a decreased platelet response to clopidogrel assessed with PRI VASP after omeprazole administration. Indeed, omeprazole is both a substrate and an inhibitor of *CYP2C19*. In contrast, in a recent study, Siller-Matula et al. (15) found no interaction between new PPIs (esomeprazole or pantoprazole) and clopidogrel response in patients with coronary artery disease. These findings suggested the preferential use of new PPIs such as pantoprazole, which are less potent *CYP2C19* inhibitors than omeprazole.

The biological interaction found between atorvastatin and clopidogrel did not show any clinical effect while the interaction was tested in large randomized trials (17,18). Two clinical reports have suggested a clinical relevance of PPI and clopidogrel interaction. Indeed, Juurlink et al. (19) suggested that among patients receiving clopidogrel after an acute myocardial infarction, concomitant therapy with a PPI other than pantoprazole was associated with a loss of the beneficial effects of clopidogrel and an increased risk of reinfarction. More recently, in a retrospective cohort study of 8,205 patients with ACS taking clopidogrel, concomitant use of clopidogrel and PPI after hospital discharge for ACS was also associated with an increased risk of adverse outcomes than use of clopidogrel without PPI, confirming that use of PPI may be associated with attenuation of the benefits of clopidogrel after ACS (20). These results suggested the clinical relevance of a biological interaction

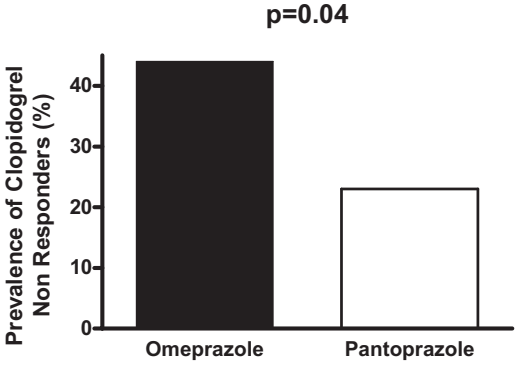

Figure 3 Prevalence of Clopidogrel Nonresponders

Prevalence of clopidogrel nonresponders (platelet reactivity index vasoactive stimulated phosphoprotein >50%) according to proton pump inhibitor treatment.

between most PPIs (e.g., omeprazole) and clopidogrel. Our present study confirms the difference between 2 different PPIs in terms of modulation of clopidogrel response. This is of great importance for daily practice because PPIs are now a standard of care for patients receiving dual-antiplatelet therapy to prevent gastrointestinal bleeding. Indeed, PPIs are recommended to prevent the risk of gastrointestinal bleeding in the latest American recommendations (21).

Study limitations. The main limitations of the present study include its small sample size and biological contents without clinical data. Additional large prospective clinical studies are required to confirm the clinical effect of this biological interaction.

Conclusions

The lack of negative effects of concomitant treatment with pantoprazole is an important finding because it may have an impact on clinical practice and suggests the preferential use of pantoprazole as PPI in patients receiving clopidogrel to avoid any potential negative interaction as described for omeprazole (13,19,20).

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Reprint requests and correspondence: Dr. Thomas Cuisset, CHU Timone, Cardiology, 264 rue Saint Pierre, Marseille, France 13385. E-mail: thomascuisset@voila.fr.

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Key Words: proton pump inhibitors ■ clopidogrel response ■ VASP assay ■ cytochrome P450 ■ coronary stenting.