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Suboptimal response to clopidogrel and the effect of prasugrel in acute coronary syndromes

L.R. Johnston [a,b,1], P.D. Larsen [b,d], A.C. La Flamme [a,b], J.M. Michel [c], M.B. Simmonds [b,c], S.A. Harding [a,b,c,*]

[a] Victoria University of Wellington, Wellington, New Zealand
[b] Wellington Cardiovascular Research Group, Wellington, New Zealand
[c] Department of Cardiology, Wellington Hospital, Wellington, New Zealand
[d] University of Otago, Wellington, New Zealand

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ABSTRACT

Background: High on clopidogrel platelet reactivity (HPR) has been associated with adverse outcomes following acute coronary syndromes (ACS). This study investigated the rate of HPR in a New Zealand ACS population and examined the effectiveness of prasugrel in reducing platelet reactivity in those with HPR.
Methods: In this prospective cohort study, 250 patients with ACS were pretreated with aspirin and clopidogrel and residual platelet reactivity was measured using whole blood multiple electrode platelet aggregometry. Twenty-seven of the patients with HPR were treated with prasugrel at the discretion of their physician, and platelet reactivity retested.
Results: Ninety-five patients (38%) had HPR. Maori and Pacific Island patients had a higher rate of HPR compared to Europeans (57% versus 35.9%, $p=0.013$). Additionally, patients with diabetes were also found to have higher rate of HPR compared to non-diabetics (50% versus 34.8%, $p=0.045$). Patients treated with a low dose clopidogrel regimen had significantly higher rates of HPR (45.4%) compared to those treated with intermediate (25.4%) or high dose regimens (26.8%, $p=0.009$). All of the 27 patients with HPR who were subsequently treated with prasugrel (60 mg) had a significant decrease in platelet reactivity (660 AU*min (565–770) before versus 230 AU*min (110–345) after, $p<0.001$), and was reduced to below the HPR cutoff in 24 (88.9%) of the patients.
Conclusions: Ethnicity, diabetes and clopidogrel dose contributed to HPR. The use of prasugrel in those with HPR resulted in a consistent and marked reduction in platelet reactivity.

1. Introduction

Dual antiplatelet therapy with aspirin and clopidogrel has been shown to improve outcomes in patients presenting with acute coronary syndromes (ACS) and in those undergoing percutaneous coronary intervention (PCI) [1–3]. However, there is wide inter-individual variability in the concentration of active metabolite and level of platelet inhibition achieved following administration of recommended doses of clopidogrel [4,5]. This variability is multi-factorial and is contributed to by non-compliance, intrinsic high platelet reactivity, drug absorption, drug interactions and genetic polymorphisms [6,7].

Multiple studies have demonstrated a clear association between a suboptimal response to clopidogrel and an increased risk of cardiovascular events in patients with ACS or undergoing PCI [5,8]. These studies suggest there is a threshold level of platelet reactivity below which ischemic events occur less frequently. Failure of clopidogrel to lower platelet reactivity below this level, referred to as high on clopidogrel platelet reactivity (HPR), is common.

Prasugrel, a third generation thienopyridine, is a more potent drug and has a more consistent effect than clopidogrel [9]. The therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel-Thrombolysis in Myocardial Infarction (TRITON-TIMI 38) trial compared clopidogrel to prasugrel in ACS patients undergoing PCI and found that use of prasugrel resulted in a reduction in ischemic events but this was at the cost of an increased risk of bleeding. To date, the utility of prasugrel in patients with HPR in has not been examined.

The aim of this study was to determine the incidence of HPR in a New Zealand ACS population. The ethnic makeup of the New Zealand population differs from those in which HPR has been previously studied in that it has a substantial portion of Maori and Pacific Islanders. We were therefore particularly interested in whether there would be differences in the occurrence of HPR between the different ethnic groups. Furthermore, we also examined the effectiveness of prasugrel in reducing platelet reactivity in those patients with HPR.

* Corresponding author at: Department of Cardiology, Wellington Hospital, Private Bag 7902, Wellington South, New Zealand. Tel.: +64 4 385 5999; fax: +64 4 385 5878.
E-mail address: Scott.Harding@ccdhb.org.nz (S.A. Harding).
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2. Methods

2.1. Study population

Patients presenting to Wellington Regional Hospital with ACS between October 2010 and March 2011 were eligible for inclusion in the study if there was an invasive approach (coronary angiography ± PCI) planned and they were adequately pretreated with aspirin and clopidogrel. An ACS was defined as symptoms suggestive of myocardial ischemia lasting > 10 min and either troponin elevation or ≥ 1 mm of new ST segment deviation or T wave inversion on an electrocardiogram in at least 2 contiguous leads. Adequate pretreatment was defined as chronic therapy with aspirin (≥ 75 mg) and clopidogrel (≥ 75 mg) and/or loading with aspirin ≥ 300 mg at least 2 h and clopidogrel ≥ 300 mg at least 6 h or prior to enrollment. Exclusion criteria included a platelet count less than 100×10^9/L, known platelet function disorder, administration of a fibrinolytic agent within 24 h of enrollment or administration of a glycoprotein IIb/IIIa receptor antagonist within a week prior to enrollment. The study was reviewed and approved by the Central Regional Ethics Committee.

2.2. Data collection

Patient demographics, clinical characteristics, medications including antiplatelet therapy, clinical management, procedural variables and in-hospital outcomes were obtained prospectively from review of the medical records and cardiac catheterization database. Ethnicity was self-identified by the patient. All aspects of clinical management, including prescription of antiplatelet therapy, were at the discretion of the attending physicians.

2.3. Blood collection and platelet function testing

Blood for platelet function testing was collected into a tube anticoagulated with Hirudin (Dynabyte, Munich, Germany) from a peripheral vein using a 21 gauge needle before angiography or in the cardiac catheterization laboratory from the arterial sheath immediately after insertion and prior to administration of heparin. Where patients with HPR were treated with prasugrel a further blood sample for measurement of platelet reactivity was taken at least 2 h post administration of a 60 mg loading dose unless a glycoprotein IIb/IIIa receptor antagonist had been administered. Cardiac enzymes including high sensitivity Troponin T (hs-TnT) and electrocardiograms were routinely performed prior to cardiac catheterization and following PCI. The collection of genetic material for testing remains a sensitive issue with some ethnicities in New Zealand. In this study, the collection of DNA samples for genotyping was not undertaken.

Platelet function testing was assessed using whole blood multiple electrode impedance platelet aggregometry with the multiplate analyser (Dynabyte, Munich, Germany) following the manufacturer's instructions. Briefly, the blood samples were tested within 30–60 min of collection. After dilution (1:2 with 0.9% NaCl solution) of the hirudin-anticoagulated whole blood and stirring for 3 min in the test cuvettes at 37 °C, ADP (adenosine diphosphate) (Dynabyte, Munich, Germany) was added with a final concentration of 6.4 mM. Aggregation was then continuously recorded for 6 min. The increase of impedance due to the attachment of platelets to the electrodes is detected for each sensor unit separately and transformed to arbitrary aggregation units (AU) that are plotted against time. Aggregation values are quantified as area under the aggregation curve expressed as aggregation units × minutes (AU∗min).

2.4. Definitions

The clopidogrel dose was defined as "high" if patients had received a 600 mg loading dose followed by a 150 mg daily maintenance dosing. Intermediate dose was defined as either a 600 mg loading dose followed by 75 mg daily maintenance or a 300 mg loading dose coupled with 150 mg maintenance dose. Low dose was defined as a 300 mg loading dose followed by 75 mg daily maintenance or chronic therapy with 75 mg daily of clopidogrel. HPR was defined as > 468 AU∗min and a cutoff value of < 188 AU∗min was used to define an enhanced response to clopidogrel. These cutoff values have been determined from a comparative analysis of the risk for bleeding and stent thrombosis across different levels of $P2Y_{12}$ receptor inhibition [10]. A periprocedural enzyme rise was defined as an increase in hs-TnT to > three times the upper reference limit (> 39 ng/L) for those with preprocedural hs-TnT levels within the normal range. In those with elevated preprocedural hs-TnT that were stable or falling a further elevation of hs-TnT > 39 ng/L was required.

2.5. Statistical analysis

Continuous variables are expressed as median and interquartile range (IQR). Categorical variables are expressed as frequencies and percentages. We compared the proportion of patients with HPR by diabetes, ethnicity and dose group using Chi-square test. Absolute values for residual platelet reactivity (AU∗min) were compared by ethnicity, diabetes and dose groups using the Kruskal Wallis test. The relationship between body mass index (BMI) and residual platelet reactivity was assessed by Spearman's correlation coefficient (*rho*). Residual platelet reactivity before and after treatment with prasugrel was compared using Wilcoxon signed rank test. All statistical tests were performed using PASW 18.0 (IBM, NY, USA).

3. Results

During the study 250 patients with ACS met the inclusion criteria and were enrolled in the study. Their baseline demographics, clinical characteristics and laboratory data are shown in Table 1. The median age was 62 (54–72) years with 74.8% being male and 20.8% having diabetes. STEMI was the presentation in 28.4%, NSTEMI in 62.4% and unstable angina in 9.2%. The majority identified themselves as European 81.2%, a further 14% as Maori or Pacific Islanders and 4.8% as other ethnicities.

Platelet reactivity was measured in all 250 patients with the multiplate analyser prior to cardiac catherterization. Of the 250 patients tested, 95 patients (38%) had HPR. Maori and Pacific Islanders had higher residual platelet reactivity (500 AU∗min (347–772) versus 380 AU∗min (250–570), p = 0.014) and a higher rate of HPR compared to Europeans (57% versus 35.9%, p = 0.013, Table 2). Patients with diabetes were also found to have higher residual platelet reactivity (435 AU∗min (290–772) versus 380 AU∗min (250–552), p = 0.029) and higher rates of HPR compared to non-diabetics (50% versus 34.8%, p = 0.045, Table 3). There was no significant correlation between BMI and residual platelet reactivity (rho = 0.1, p = 0.1). Mean residual platelet reactivity and rates of HPR were also not affected by concomitant treatment with a proton pump inhibitor or the type of ACS at presentation.

Although all patients were pretreated with aspirin and clopidogrel, a variety of clopidogrel dosing regimens were used with the majority of patients (61.6%) being treated with a low dose regimen. To understand the relationship between clopidogrel dose and residual platelet reactivity, we compared the rates of HPR in patients who received low, intermediate, and high dose regimens (Table 4). Our findings show that patients treated with a low dose regimen had significantly higher rates of HPR compared to those treated with intermediate or high dose regimens (p = 0.009). Additionally, the mean residual platelet reactivity decreased with increasing clopidogrel dose (p = 0.007).

Table 1
Patient baseline demographics, clinical characteristics and laboratory data.

	N = 250	HPR	No HPR	p value
		(n = 95)	(n = 155)	
Age (years)	62 (54–72)	62.0 (55–71)	61.0 (53–72)	0.679
Male, n (%)	187 (74.8)	73 (76.8)	114 (73.5)	0.560
BMI	28 (19–56)	29 (26–33)	27 (25–31)	0.066
Ethnicity, n (%)				
European	203 (81.2)	71 (74.7)	132 (85.2)	0.041
Maori and Pacific Islander	35 (14)	20 (21.1)	15 (9.7)	0.019
Other	12 (4.8)	4 (4.2)	8 (5.2)	0.649
Risk factors, n (%)				
Hypertension	145 (58.0)	55 (57.9)	90 (58.1)	0.979
Dyslipidemia	137 (54.8)	53 (55.7)	84 (54.2)	0.806
Diabetes	52 (20.8)	26 (27.3)	26 (16.7)	0.045
Current smoker	65 (26.0)	27 (28.4)	38 (24.5)	0.494
Medical history, n (%)				
Previous MI	56 (22.4)	26 (27.4)	30 (19.4)	0.140
Previous PCI	40 (16.0)	21 (22.1)	19 (12.3)	0.039
Previous CABG	20 (8.0)	9 (9.5)	11 (7.1)	0.501
Clinical presentation, n (%)				
STEMI	71 (28.4)	28 (29.5)	43 (27.8)	0.768
NSTEMI	156 (62.4)	58 (61.1)	98 (63.2)	0.731
Unstable angina	23 (9.2)	9 (9.5)	14 (9.1)	0.919
Laboratory data				
Creatinine (μmol/L)	88 (76–102)	89 (77–102)	88(74–102)	0.357
Platelet count (10^9/L)	220 (187–267)	223 (190–278)	217 (187–264)	0.135
PPI use, n (%)	65 (26.0)	22 (23.2)	43 (27.7)	0.423
Clopidogrel dosing				
High	41 (16.4)	11 (11.6)	30 (19.4)	0.107
Intermediate	55 (22.0)	14 (14.7)	41 (26.5)	0.30
Low	154 (61.6)	70 (73.7)	84 (54.2)	0.003