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Interventional Medicine & Applied Science, Vol. 8 (4), pp. 135–140 (2016) ORIGINAL PAPER

Assessment of platelet function in patients receiving tirofiban early after primary coronary intervention

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(Received: August 31, 2016; Revised manuscript received: December 11, 2016; Accepted: December 11, 2016)

Abstract: *Background:* Following percutaneous coronary intervention, combined antiplatelet therapy is necessary. Platelet function testing (PFT) has prognostic value and may be applied in the risk assessment of acute coronary syndrome. In case of combined antiplatelet therapy, PFT may require special laboratory methods, as different antiplatelet agents may influence test results. *Materials and methods:* Platelet functions were measured in stent thrombosis-segment elevation myocardial infarction patients receiving aspirin, clopidogrel, and tirofiban. The first sampling was obtained immediately after the termination of administration of tirofiban. The second sample was drawn at a randomly assigned time between 1 and 6 h. The third sampling was done after a minimum of 24 h of tirofiban cessation. Adenosine diphosphate (ADP)- and thrombin receptor-activating peptide (TRAP)-induced aggregations were measured. *Results:* Thirty-seven patients were included. Both TRAP- and ADP-induced aggregation values were significantly lower immediately after tirofiban termination, than after 24 h [TRAP: 26.41 ± 25.00 units (U) vs. 109.86 ± 23.69 U, $p < 0.0001$; ADP: 17.43 ± 10.10 U vs. 43.92 ± 23.35 U, $p \leq 0.0001$]. Elimination half-life of tirofiban and clopidogrel were 1.34 ± 0.49 and 1.269 ± 0.78, respectively. *Conclusion:* ADP-induced residual platelet reactivity is significantly influenced by the presence of concurrent glycoprotein IIb/IIIa inhibitor. In patients receiving combined antiplatelet treatment, ADP-receptor-specific efficiency measurements are valid only after total elimination of GPIIb/IIIa inhibitors.

Keywords: clopidogrel, tirofiban, platelet function testing, ADP reactivity, combined antiplatelet treatment

Introduction

Cardiovascular diseases are considered as the leading cause of death in developed countries. Percutaneous coronary intervention (PCI) and the application of stents resulted in substantial breakthrough in the treatment of coronary heart disease, especially in patients with acute coronary syndromes (ACSs). Because of the prothrombotic effect of the procedure and the underlying disease, patients undergoing PCI and stent implantation have a high risk for developing stent thrombosis (ST). Consequently, an intensified combined antiplatelet therapy is required at the time of the PCI that is tapered gradually afterward [1, 2]. In addition to aspirin, adenosine diphosphate (ADP) $P2Y_{12}$ receptor blockers and platelet glycoprotein (GP) IIb/IIIa (also known as integrin αIIbβ3) inhibitors may be a part of these combinations. As for ADP blockers, newer generation agents such as prasugrel and ticagrelor are the first choices of treatment in patients with ACSs, as they provide more active and consistent platelet inhibition. However, because of the financial and regulatory reasons, the availability of these drugs is not optimal, thus the earlier generation ADP blocker clopidogrel is still frequently used [3]. Clopidogrel is a prodrug with variable action. In cases with high ischemic risk, measurement of the residual ADP reactivity may be considered. Although current guidelines discourage the routine testing of patients after stent

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implantation, platelet function testing (PFT) has a clear prognostic value and may be applied in the risk assessment of ACS cases [1, 4]. Furthermore, in Hungary, prasugrel is only reimbursed at the level of 70% in ACS patients with diabetes and with verified impaired response to clopidogrel. GPIIb/IIIa receptor antagonists, including tirofiban, provide an immediate, very intensive inhibition of platelet aggregation, but being parenteral agents, they are used only temporarily in cases with high thrombotic burden and thrombotic risk. The combined use of antiplatelet agents may expose special requirements for laboratory testing, as antiplatelet agents may influence the test results despite their different mechanisms of action.

We aimed to investigate the effect of combined treatment with ADP receptor blockers and GPIIb/IIIa inhibitor tirofiban on ADP-receptor-specific platelet function tested by Multiplate impedance aggregometry in patients with ST-segment elevation myocardial infarction (STEMI) undergoing PCI.

Materials and Methods

Patients

We recruited ACS patients with STEMI admitted for primary angioplasty in whom coronary intervention with stent implantation was performed and tirofiban treatment was initiated. Exclusion criteria were age over 75 years, chronic treatment with thienopyridines, loading dose of clopidogrel lower than 600 mg prior to PCI, concomitant oral anticoagulant therapy, history of stroke or transient ischemic attack, intolerance or allergy to clopidogrel/aspirin, known bleeding disorders, and low platelet count ($<100 \times 10^9$/l). All patients received 600 mg of clopidogrel and 300 mg of aspirin at the first medical contact when diagnosis of STEMI was established. Coronary interventions were performed immediately after coronary angiography revealing significant coronary stenosis feasible for stent implantation. An intravenous bolus of 25 μg/kg of tirofiban was administered for all PCI patients according to the operator's decision, in case of total thrombotic occlusion of a main coronary and/or significant thrombus burden. After PCI, tirofiban was continued at a rate of 0.55 μg/kg/min maintenance dose for 6 h. From the first day after PCI, 100 mg of aspirin was co-administered with 75 mg of clopidogrel in all patients. The study protocol was approved by the regional ethics committee (Approval no.: 3551) and patients gave written consent for participation.

Blood sampling and aggregometry

Three milliliters of blood were drawn from each patient from a peripheral vein into hirudin-coated vacuum tubes (Becton and Dickinson, Munich, Germany). The first sampling and measurement were done immediately after the termination of administration of GPIIb/IIIa inhibitor tirofiban (Sample A), while a second sample was drawn at a randomly assigned time between 1 and 6 h (Sample B) and a third sample after a minimum of 24 h of tirofiban cessation (Sample C). Multiple electrode aggregometry (Multiplate, Roche Diagnostics GmbH, Mannheim, Germany) was used for platelet function assessments [5]. From each patient's sample, 300 μl of whole blood was stirred at 37 °C between two platinum wire electrodes, set at a fixed distance. We aimed to measure the efficiency of clopidogrel and tirofiban. For measuring clopidogrel efficacy, ADP (0.2 mM, Roche) was used as agonist agent. Efficiency of tirofiban was determined indirectly, as the overall platelet function independent from ADP reactivity. Thrombin receptor-activating peptide (TRAP; 0.2 mM, Roche) was administered as the agonist agent in the determination of overall platelet reactivity. The platelet aggregation was measured automatically by Multiplate device, calculating the area under the curve from the function of impedance to time.

Statistical analysis

Continuous variables are presented as means ± SD. Categorical variables are expressed as frequencies and percentages. Data were analyzed according to their normal distribution on the Kolmogorov–Smirnov goodness-of-fit test. Paired *t*-tests were used for the comparison of normally distributed continuous variables in the same group between time points. Non-normally distributed paired variables were compared using the Wilcoxon matched pairs test. Hyperbolic curve fittings to platelet reactivity to time were prepared assuming single ligand–receptor interaction. A p value <0.05 was considered statistically significant in all analyses. Statistical analyses were performed with GraphPad InStat 3 version and GraphPad Prism 6 version statistical packages (GraphPad Software, San Diego, CA, USA).

The authors of this manuscript have certified that they comply with the principles of ethical publishing [6].

Results

Patient characteristics

Between January 1, 2013 and December 31, 2013, a total of 1,252 patients with ACS were admitted to the Heart Institute at the University of Pécs for urgent coronary angiography. Subsequent to coronary angiography, 632 patients underwent PCI with successful stenting. Thirty-seven patients met the inclusion criteria and were included in this study. *Table I* shows the baseline clinical

Table I Patient data

Baseline clinical characteristics ($n = 37$)	
Age, mean ± SD (years)	62.91 ± 8.92
Male gender, *n* (%)	22 (59.5)
Diabetes mellitus, *n* (%)	10 (27.0)
Arterial hypertension, *n* (%)	26 (70.2)
Dyslipidemia, *n* (%)	27 (73.0)
Smokers, *n* (%)	18 (48.6)
Prior PCI, *n* (%)	2 (5.4)
Prior coronary artery bypass graft, *n* (%)	3 (8.1)
Prior MI, *n* (%)	5 (13.5)
PCI procedure	
Bare-metal stent, *n* (%)	31 (83.8)
Total stent length, mean ± SD (mm)	44.0 ± 13.2
Stent count/patient, mean ± SD (*n*)	2.1 ± 0.82
Laboratory findings 1 day after PCI	
Hemoglobin (g/dl)	138.0 ± 15.0
Leukocyte count (g/l)	11.56 ± 3.3
Platelet count (g/l)	245.0 ± 48.0
Creatinine (μmol/l)	76.8 ± 30.0
High-sensitivity C-reactive protein (mg/l)	9.5 ± 19.5
Discharge medication	
Aspirin, *n* (%)	37 (100.0)
Angiotensin-converting enzyme inhibitor/ angiotensin receptor blocker, *n* (%)	33 (89.2)
Beta blocker, *n* (%)	32 (86.5)
Proton pump inhibitor, *n* (%)	34 (91.9)
Statin, *n* (%)	36 (97.3)

characteristics of the recruited patients and data regarding therapy.

Platelet aggregation profiles

Both TRAP- and ADP-induced aggregation values were significantly lower in samples obtained immediately after the termination of tirofiban (Sample A), than in the samples after 24 h (Sample C) [TRAP: 26.41 ± 25.00 units (U) vs. 109.86 ± 23.69 U, $p < 0.0001$; ADP: 17.43 ± 10.10 U vs. 43.92 ± 23.35 U, $p \leq 0.0001$] *(Fig. 1)*. Residual platelet reactivity was demonstrated depending on the time after the termination of tirofiban, and performing curve fittings, K_d values were determined: in case of TRAP and ADP induction, these estimates were 1.34 ± 0.49 (95% CI: 0.35–2.32; $B_{max} = 112.5 \pm 8.93$) and 1.269 ± 0.78 ($B_{max} = 51.15 \pm 6.67$), respectively *(Fig. 2)*.

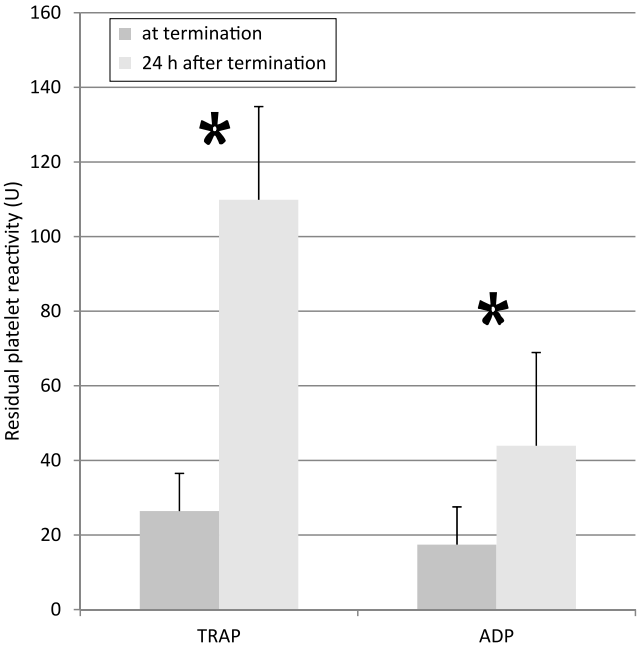

Fig. 1. Mean residual platelet reactivity at the time and 24 h after the termination of tirofiban administration in patients receiving combined antiplatelet therapy after PCI. Tirofiban effectiveness was measured by TRAP, while clopidogrel efficiency was monitored by ADP administration. ADP: adenosine diphosphate, TRAP: thrombin receptor-activating peptide, U: unit, *$p < 0.00001$

Discussion

This study found that ADP-induced platelet reactivity values, detected by Multiplate electrode aggregometry may be influenced by tirofiban action, resulting in lower values of ADP-induced residual platelet reactivity. Consequently, this interaction may conceal the real residual ADP reactivity, thus ADP receptor-specific efficiency measurements are only possible after the total elimination of GPIIb/IIIa inhibitor tirofiban.

Current recommendations based on 2014 European Society of Cardiology/European Association for Cardio-Thoracic Surgery (ESC/EACTS) Guidelines on myocardial revascularization only support the use of GPIIb/IIIa inhibitors in a smaller group of patients with myocardial infarction (MI), as an adjunctive bail-out medication. Despite the decreasing use of GPIIb/IIIa inhibitors and – as our study shows – its influence on the measurements of the blockage efficiency of ADP receptors, it is important to note GPIIb/IIIa inhibitors' beneficial contribution to the treatment of certain cases of MI. In a meta-analysis including 20,006 patients, tirofiban was significantly more effective, than placebo at reducing the risk of mortality (OR = 0.68; $p = 0.001$) or the composite of death and MI (OR = 0.69; $p < 0.001$) at 30 days [7]. The INFUSE-AMI (Intracoronary Abciximab and Aspiration Thrombectomy in Patients With Large Anterior

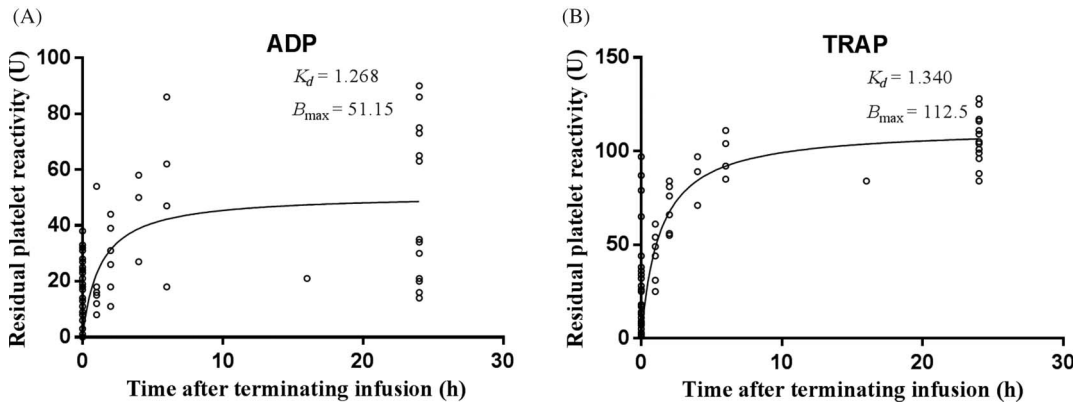

Fig. 2. Residual platelet reactivity in the function of the time after the termination of tirofiban administration in patients receiving combined antiplatelet therapy. ADP: adenosine-diphosphate, TRAP: thrombin receptor-activating peptide, K_d: pharmacodynamic half time, B_{max}: maximal platelet reactivity

MI) study also provides data strengthening the role of GPIIb/IIIa inhibitors. In this trial, the infarct size at 30 days was smaller when the patients underwent both thrombus aspiration and application of intracoronary IIb/IIIa inhibitor abciximab, and larger if only thrombus aspiration was performed (mean % of the left ventricle 14.7% vs. 18.6%, $p = 0.03$). The FABOLUS PRO (Facilitation through Aggrastat By drOpping or shortening Infusion Line in patient with STEMI compared to or on top of PRasugrel given at loading dOse) trial also fortifies the positive effect of GPIIb/IIIa antagonists: tirofiban administered (as bolus only or bolus followed by 2-h infusion) to patients with MI undergoing coronary stenting together with either clopidogrel or prasugrel, leads to a significantly higher degree of platelet inhibition compared with prasugrel alone [8, 9].

With the advent of new-generation ADP $P2Y_{12}$ inhibitors, the importance of GPIIb/IIIa receptor blockers has been reduced in the adjunctive therapy of coronary interventions. This is despite the fact that these drugs were frequently applied in the major ACS trials of prasugrel and ticagrelor. Tirofiban was co-administered as adjuvant in 54.4% of patients in the PLATO (A Study of Platelet Inhibition and Patient Outcomes) trial and in 53.2% of patients in the TRITON-TIMI 38 (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel–Thrombolysis in MI 38) trial [10, 11].

Current recommendations based on 2014 ESC/EACTS Guidelines on myocardial revascularization offer the new-generation $P2Y_{12}$ inhibitors for antiplatelet therapy as the first choice drugs in ACS. Although these drugs are proven to have higher efficacy, on the other hand, the risk of bleeding is also increased [12].

Because of financial limitations, clopidogrel is still the most frequently used $P2Y_{12}$ inhibitor in Hungary. Numerous reports have found that the antiplatelet efficacy of clopidogrel exhibits considerable interindividual variability [2, 13]. High platelet reactivity (HPR), also called as high on-treatment platelet reactivity, during clopidogrel therapy indicates persistent response of the $P2Y_{12}$ receptor, which is based on one measurement of on-treatment platelet reactivity. Observational studies have demonstrated a strong correlation between HPR and recurrent ischemic events in stented patients [14, 15]. According to the results of a meta-analysis ($n = 9{,}187$), patients with high on-clopidogrel platelet reactivity after PCI, detected by an ADP-specific laboratory assay, are at a higher risk for cardiovascular death, non-fatal MI, ST, and recurrent ischemic events, thus HPR considered as a strong predictor for those after PCI [4]. Consequently, we can conclude that PFT plays an important role in monitoring of clopidogrel therapy after PCI; furthermore, HPR – detected by an ADP-specific laboratory assay for 1 year – serves as the condition of the reimbursement of prasugrel in Hungary.

ADP values measured during tirofiban activity were significantly lower than after elimination of the drug. Since ADP-receptor blockers, including clopidogrel selectively and irreversibly inhibit the $P2Y_{12}$ purinoreceptor throughout the lifespan of the platelets. The difference is explained by the fact that the simultaneously present GPIIb/IIIa inhibitor tirofiban influences the efficacy measurement of ADP receptor inhibitors. Therefore, on the first day, ADP values are artificially lower, thus these laboratory results do not reflect the real efficiency of ADP receptor inhibition and incorrectly indicate a low risk for further thrombotic events. In addition, because of the falsely measured clopidogrel efficacy, patients with an underlying insufficient clopidogrel reaction are excluded from reimbursed treatment with prasugrel.

According to our data, elimination half-life ($T_{1/2}$) of tirofiban can be reliably calculated to be less than 2.5 h. Twenty-four hours after the termination of tirofiban, the drug is totally eliminated [five times $T_{1/2} = 6.7$ h (95% CI: 1.75–11.6)]; thus, platelet GPIIb/IIIa receptors are

released from inhibition. Inasmuch as the receptors' function is regained and they are able to function, TRAP values should raise – our data support the same conclusion: increased TRAP values could be seen in Sample C. The very first time of ADP-receptor-specific efficiency measurement showing adequate data should be obtained at least 6.7 (95% CI: 1.75–11.6) h after the termination of the GPIIb/IIIa inhibitors, practically after 12 h.

Examining the changes in residual platelet reactivity after ADP stimulation, measured values correlate in parallel with the elimination of tirofiban. In addition, as the GPIIb/IIIa inhibitor's effect subsides, the variability between individuals on clopidogrel treatment becomes increasingly apparent – but these differences are masked by the perioperative administration of tirofiban. As demonstrated in *Fig. 2A*, two groups with adequate and inadequate response separate to the 24 h time point. Values above the curve belong to patients with HPR. On the other hand, patients' data under the curve demonstrate normal post-treatment platelet reactivity (NPR). Application of ADP receptor blocker clopidogrel is only effective in the NPR group of patients. In contrast, in the HPR group of patients (based on Hungarian and European consensus recommendation for Multiplate electrode aggregometry below 46 U), application of clopidogrel is ineffective, thus adequate change in drug therapy is advocated [5, 16].

Conclusion

We demonstrated that ADP-receptor-specific residual platelet reactivity is significantly influenced by the presence of concurrent GPIIb/IIIa inhibitor. Based on our results, in cases of patients undergoing PCI and receiving combined antiplatelet treatment, ADP-receptor-specific efficiency measurements are valid only after the total elimination of GPIIb/IIIa inhibitors. The first measurement should be obtained 12 h after the termination of the GPIIb/IIIa inhibitors for valid results to be obtained. In case of a need of an earlier measurement, methods other than ADP-induced aggregation or development of algorithm considering the total platelet reactivity and the time elapsed from the cessation of GPIIb/IIIa infusion may be required.

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Funding sources: The research was supported by the University of Pécs, Hungary (AOK-KA 2015-17 to András Komócsi).

Authors' contribution: PK: data collection, data analysis, and manuscript development. DA: development of concept, data collection, data analysis, and scientific overview. AT and MT-F: scientific overview. AK: development of concept, data analysis, scientific overview, and final supervision. PK and DA contributed equally to the manuscript. All authors had full access to all data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Conflict of interest: The authors declared that they have no conflict of interest.

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