Journal of Thrombosis and Thrombolysis 11,151–154,2001.

Clinical Application of Procedural Platelet Monitoring during Percutaneous Coronary Intervention among Patients at Increased Bleeding Risk

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Abstract. **The goal of platelet function testing in the catheterization laboratory is to provide information about the platelet contributions to the risk of thrombotic or hemorrhagic events and optimization of anti-platelet therapy for percutaneous interventions. We present several illustrative cases in which platelet monitoring with the Rapid Platelet Function Assay (RPFA^{TM}, Accumetrics) was used to guide dosing of a glycoprotein (GP) IIb/IIIa inhibitor for coronary and peripheral intervention among patients at increased bleeding risk.**

Key Words. **coronary artery disease, percutaneous intervention, platelet, abciximab, GP IIb/IIIa inhibitor**

Introduction

The goal of platelet function testing in the catheterization laboratory is to provide information about the platelet contributions to the risk of thrombotic or hemorrhagic events and optimization of anti-platelet therapy for percutaneous interventions (PCI). Important clinical questions prior to coronary interventions are whether an antiplatelet agent is having the desired effect on platelet inhibition (efficacy) and whether the patient has sufficient residual platelet function to avoid bleeding (safety). Table 1 The role of aspirin and thienopyridines is well established in management of coronary artery disease and in the setting of coronary interventions. The last several years have demonstrated the unequivocal efficacy of intravenously administered platelet GP IIb/IIIa antagonists in the management of acute coronary syndromes and in the setting of PCI.

To date, approximately 18,000 patients undergoing PCI have been studied in clinical trials with GP IIb/IIIa inhibitors [1,2]. Overall the 30-day ischemic composite endpoint of death, myocardial infarction, and urgent target vessel revascularization has been reduced 35–50 % with GP IIb/IIIa agents targeting $\geq 80\,\%$ platelet inhibition as in the EPIC study [3]. Patients were excluded from these randomized clinical trials if they had increased risk of bleeding (eg. thrombocytopenia or receiving oral anticoagulants). Since then a rapid point-of-care assay measuring platelet aggregation has become clinically available. As such, patients at an increased risk for bleeding with IIb/IIIa inhibitors might receive a net benefit from these agents if they could be administered in a safe-dosing manner. In this manuscript, we present several illustrative cases in which platelet monitoring with the Rapid Platelet Function Assay (RPFA^{TM}, Accumetrics) was used to guide dosing of a GP IIb/IIIa inhibitor for coronary intervention among patients at increased bleeding risk but deemed to otherwise need IIb/IIIa therapy. Normally during GP IIb/IIIa therapy administration, 80–90 % inhibition of platelet aggregation is achieved, meaning that only approximately 10,000 receptors per cell are unaffected. If patients with thrombocytopenia or other coagulation defect could be inhibited with low-dose IIb/IIIa treatment to a similar level of platelet inhibition, we may potentially expect similar improvement in clinical outcomes and not particularly increase risk of bleeding. While we do not endorse the routine use of GP IIb/IIIa therapy for patients at increased risk of bleeding, a subset of patients with high-risk lesions may benefit from such therapy.

Methods

Rapid platelet function assay

The *Ultegra* – RPFA^{TM} is an automated, whole-blood, cartridge-based, point-of care device that allows for the rapid and reproducible evaluation

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Table 1. *List of scenarios in which platelet monitoring would be clinically useful (adapted from (8))*

Patient
Confirm $\geq$ 80 % aggregation inhibition
- Prior to PCI
- In patients with refractory ischemia on IIb/IIIa inhibitors
- Interruption of intravenous therapy
- Abnormal platelet count
- Renal insufficiency
- High or low body-weight

Clinical
Bleeding
- Confirm excess inhibition
- Guidance during reversal of therapy

Emergent Surgery
- Confirm $\leq$ 50 % aggregation inhibition
- Guidance to reverse therapy if needed

Other
Drug-specific
- Switching among intravenous agents
- Transition from intravenous to oral agents
- Combination with other antiplatelet/anticoagulants

of platelet function in patients treated with GP IIb/IIIa inhibitors. It is designed to assess platelet function utilizing the ability of activated platelets to bind fibrinogen [4]. Fibrinogen-coated polystyrene microparticles agglutinate in whole blood in proportion to the number of unblocked platelet GP IIb/IIIa receptors. Pharmacologic blockade of GP IIb/IIIa receptors prevents this interaction and therefore diminishes agglutination in proportion to the degree of receptor blockade achieved. Because the speed of bead agglutination is more rapid and reproducible if platelets are activated, the thrombin receptor-activating peptide iso-TRAP [(iso-S)FLLRN] is incorporated into the assay. As the platelets interact with the fibrinogen-coated beads resulting in agglutination, there is a progressive increase in light transmission. The rate of agglutination is quantified as the slope of the change of absorbance over a fixed time interval and reported as millivolts per 10 s (mV/10 s) [5].

Results

Table 2 lists five case scenarios in which reduced dose abciximab was used to achieve target ($>$ 80 %) inhibition of platelet aggregation. Baseline platelet counts, baseline platelet aggregation units, post-abciximab platelet aggregation units and percentage inhibition of platelet aggregation is shown for each individual patient.

Case 1. KA, was a 44 year-old female with unstable angina, with past medical history significant for coronary artery disease with previous angioplasty of the left anterior descending artery in 1997, systemic lupus erythematosus with severe thrombocytopenia and lupus nephritis. On the day of admission her platelet count was 14,000/μL, and she received a six-unit platelet transfusion. The patient was taken to the catheterization laboratory on July 7, 2000, and diagnostic angiography revealed high-grade lesions in the mid-portion of her left anterior descending artery (LAD) and in the mid-portion of her right coronary artery (RCA). The platelet count on the day of the procedure was 74,000/μL. After obtaining a baseline platelet inhibition measurement with the RPFA, 30 % of the recommended abciximab bolus was administered. The RPFA assay after abciximab showed 89 % inhibition of platelet aggregation (%IPA Table 2). PCI was successfully performed with stent placement to the mid LAD and RCA. The platelet count on the following day was 23,000/μL (her baseline level), and there was no evidence of bleeding. There was no EKG or enzyme evidence (CK-MB $>$ 3X) of a periproce-

Table 2. *Characteristics of patients treated with reduced dose abciximab and platelet monitoring*

Case #	Body weight (kg)	Platelet count	Abciximab dose (mg) [% of std]	PAU (pre)	PAU (post)	%IPA	Other factors
1	80.2	74,000	6.0 [30 %]	140	16	88	Lupus
2	94.1	156,000	17.6 [75 %]	180	18	90	INR 1.97
3	56.0	55,000	7.0 [50 %]	163	11	93	
4	101.2	73,000	12.7 [50 %]	155	19	88	
5	76.4	114,000	14.2 [75 %]	190	35	81	RICA

Recommended abciximab dosage: 0.25 mg/kg bolus and infusion of 0.125 μg/kg/min (10 μg/min maximum).
PAU = Platelet aggregation units.
RICA = Right internal carotid artery.
IPA = Inhibition of platelet aggregation.

dural MI. The patient was discharged home on lifelong aspirin (81 mg) and a two-week course of clopidogrel.

Case 2. RH, a 75-year old male with unstable angina, presented on April 23, 2000. His past medical history was significant for hypertension, hyperlipidemia, renal insufficiency and atrial fibrillation. The patient had been on warfarin for atrial fibrillation for three years. His warfarin was stopped on April 23, 2000 and intravenous heparin started. Despite cardioversion to sinus rhythm and heart rate control, the patient had recurrent rest symptoms, and diagnostic angiography on April 25, 2000 revealed high-grade lesions in the proximal portion of his left circumflex artery (LCX) and in the mid RCA. His international normalized ratio (INR) on the day of the procedure was 1.97, suggesting persistent warfarin effect. The patient's creatinine was 1.9 and the estimated glomerular filtration rate was 34 ml/min, consistent with his history of renal insufficiency. Because of unstable angina, PCI was undertaken and the patient was given 75% of the usually recommended abciximab dosage and comparing pre- and post-abciximab RPFA measurements showed 92% IPA. The patient received a stent to the LCX and the RCA and had an uneventful hospital course. There was no EKG or enzyme evidence (CK-MB $>$ 3X) of a peri-procedural MI. He was discharged the following morning on aspirin, warfarin, and a four-week course of clopidogrel.

Case 3. BJ, a 76-year-old female admitted to the hospital with unstable angina, had history of hypertension, hyperlipidemia and coronary artery disease. She had coronary artery bypass grafting in 1992 with grafts to the LAD, diagonal branch of LAD and the RCA. Diagnostic angiography was performed the following day, which revealed severe obstruction in the saphenous vein graft to the RCA. Her baseline platelet count was 55,000/μL, and she was given 50% of the usual weight-based abciximab bolus and infusion. This resulted in 93% IPA, and PCI with stenting was performed to the graft to the RCA. There was no EKG or enzyme evidence (CK-MB $>$ 3X) of a peri-procedural MI. The patient was discharged the following day on aspirin and a four-week course of clopidogrel. The post-procedural platelet count was 51,000/μL.

Case 4. JP, a 78-year old gentleman who presented to the hospital with class III angina, had history of hypertension, diabetes mellitus and hyperlipidemia. Stress thallium testing revealed extensive ischemia in the anterolateral, lateral, posterior and posterolateral region of the left ventricle. Diagnostic angiography revealed severe lesions in the diagonal branch of the LAD and the mid LCX. His platelet count was 73,000/μL and he was given 50% of the recommended abciximab bolus. Following this his platelet aggregation was 88% inhibited. Revascularization was performed with a stent placement to the diagonal branch of the LAD and the mid-LCX. No EKG or enzyme evidence (CK-MB $>$ 3X) of a peri-procedural MI was found. He was discharged to home the next day on aspirin and a four-week course of clopidogrel.

Case 5. GR, an 86-year-old gentleman with severe right internal carotid stenosis, presented for elective carotid stenting. His past history was significant for hypertension, hyperlipidemia, diabetes mellitus, and coronary artery disease. The patient had a baseline platelet count of 114,000 and was given 50% of the usual abciximab bolus. After the 50% bolus, the platelet aggregation was 57% inhibited and an additional 25% bolus was given (75% total). This achieved 81% IPA. Stent placement in the right internal carotid artery was successful and the patient was discharged to home the next day on aspirin and a four-week course of clopidogrel.

Discussion

While abciximab is not recommended for patients with thrombocytopenia and patients on oral anticoagulants, the current cases demonstrate that abciximab might potentially be safely and effectively used in some patients with reduction of abciximab dose and rapid platelet monitoring. For these five patients, the average platelet count was 94,000/μL, and the pre-abciximab platelet aggregation unit (PAU) was 165.6 ± 19.8. The GOLD investigators, serially measured RPFA among 500 patients undergoing PCI with IIb/IIIa therapy [6]. The baseline PAU in our patient series is substantially lower than that observed by the GOLD investigators among the 500 patients with normal platelet counts (165.6 ± 19.8 vs 208.92 ± 24.65, $p = 0.002$) [7]. In our first case, 30% of the recommended dosage obtained adequate platelet inhibition. Full-dose abciximab without platelet monitoring might otherwise have led to bleeding-related problems. This patient was able to obtain the benefits of GP IIb/IIIa therapy during PCI safely by rapid point-of-care monitoring. In the second case because of oral anticoagulation, the operators were concerned about bleeding risk and a fractional dose of abciximab was used instead of the full dose. In the subsequent three cases reduced-dose abciximab was used because of relative thrombo-

cytopenia with adequate platelet inhibition for PCI needed. Patients with a history of stroke or those undergoing cerebrovascular interventions may be at higher risk of intracranial hemorrhage with GP IIb/IIIa antagonists and careful platelet monitoring may be particularly important in this group of patients.

These cases highlight some of the clinical scenarios in which platelet monitoring can be useful. Use of parenteral platelet GP IIb/IIIa antagonists has been consistently shown to reduce the risk of thrombotic complications in the setting of acute coronary syndrome and PCI. However, there are several groups of patients who might be at higher bleeding risk with these agents. The ability to rapidly and reproducibly monitor the effects of these agents in individual patients is important to optimizing and extending their use. It should be emphasized, however, that the patients presented here are currently not considered candidates for GP IIb/IIIa inhibitor use, and we do not advocate the routine use of GP IIb/IIIa inhibitors in this patient population. However, the ability to rapidly measure platelet aggregation inhibition may allow the use of these beneficial agents at a reduced dose in select patients at increased risk of bleeding from thrombocytopenia on use of oral anticoagulants.

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