Does glycoprotein IIB/IIIA resistance exist?

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Platelet function testing is not embedded into routine clinical practice, because no optimal, easy, reproducible and multipathway platelet aggregation test can be accomplished in vitro. Only recently, the relationship between the level of platelet aggregation inhibition by platelet inhibitors and clinical outcome in acute myocardial infarction became more clear.¹⁻⁵ High platelet reactivity was found in patients who experienced stent thrombosis, and patients with clopidogrel resistance were at increased risk of recurrent atherothrombotic events.^{1,2} Furthermore, in ST-elevation myocardial infarction (STEMI) increased levels of platelet aggregation were found compared with unstable angina or control patients.⁴ In a thrombolysis study, higher platelet receptor occupancy was coupled with better angiographic and electrocardiographic outcome.³ Finally, in STEMI patients undergoing primary percutaneous intervention (PCI), higher levels of platelet aggregation inhibition by abciximab were recently found to be associated with better myocardial reperfusion.⁵ Therefore, measuring platelet function in patients with an acute coronary artery syndrome is gaining interest to select patients at high risk of an unfavourable thrombotic event.

In the study by Van Werkum et al. in this edition of the Journal, platelet function is measured in patients with an acute coronary syndrome randomised to abciximab, high-dose tirofiban or placebo. Only 40 to 50% of platelets were inhibited in the abciximab-treated patients, whereas platelet inhibition reached 80% in the patients treated with high-dose tirofiban.⁶ The authors refer to studies using TARGET trial dosing, in which low-dose tirofiban achieved only 60 to 66% platelet inhibition and resulted in more procedure-related ischaemic events than abciximab,

which produced 90 to 95% platelet inhibition (using optical light aggregometry).^{7,8} Therefore, Van Werkum et al. used the high-dose tirofiban instead, for comparison with abciximab and placebo. Nevertheless, even in the high-dose tirofiban, there was still considerable platelet aggregation in vitro (20% of platelets). In early dose-finding studies a level of platelet aggregation inhibition of >80% was strived for.^{9,10} The study results of Van Werkum et al. show striking similarities with a previous study which used the same platelet function test.¹¹ Again only 46% platelet aggregation inhibition was found in the abciximab group and 86% platelet aggregation inhibition in the high-dose tirofiban group. The explanation for this 'drug resistance' might be related to the dose of the drug or the underlying disease. This lack of optimal platelet inhibition could be described as glycoprotein IIB/IIIA 'resistance'. However, does resistance against an antiplatelet therapy exist?

Platelet function tests and resistance

In the past years the terms aspirin resistance and clopidogrel resistance have emerged to describe different phenomena: 1) inability to prevent thrombotic complications, 2) a platelet aggregation inhibition, measured by in vitro platelet function tests, below certain cut-off values, 3) insufficient inhibition of plasma or urinary biochemical markers for platelet aggregation. 'Resistance' as a description of inter-individual variability in the outcome of a platelet function test is incorrect, because the definition of resistance is dependent on a cut-off value. The cut-off values for aspirin or clopidogrel resistance are highly variable in the literature. Above all, most of the cut-off values are defined by measuring healthy volunteers. The response of patients with unstable coronary artery disease or myocardial infarction is, however, different from the outcome of a platelet function test in healthy volunteers.¹² In the setting of an acute coronary syndrome, hyperaggregable platelets circulate which require more extensive antiplatelet therapy. For example, in one of the most recent articles by Gurbel et al., the cut-off value for the bleeding time measured by PFA-100 collagen cartridge was 193 seconds.¹³

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This value, however, is derived from the manufacturers and is based on a normal value in healthy volunteers. Since these values can hardly be extrapolated to patients with coronary artery disease, defining aspirin or clopidogrel resistance based on cut-off values derived from healthy volunteers is inadequate. Another argument against describing the interindividual platelet aggregation response to an antiplatelet drug as 'resistant' is the normal pharmacodynamic and pharmacokinetic variability.¹⁴ It seems more likely that the interindividual response to aspirin and clopidogrel is a normally divided bell-shaped reaction, depending on both pharmacodynamic and pharmacokinetic variability and the underlying disease and type of platelet function test used, rather than a separate group of patients unable to respond to the drug.¹⁵ Therefore, also glycoprotein IIB/IIIA 'resistance' is probably better described as a normal interindividual response to glycoprotein IIB/IIIA blockers.

Conclusion

Just as aspirin and clopidogrel 'resistance', glycoprotein IIB/IIIA blocker 'resistance' is very much dependent on the type of assay or type of platelet function test used. An internationally accepted definition of resistance to antiplatelet drugs is lacking. Therefore, it remains to be determined whether results of platelet function testing can be used as surrogate for the clinical effectiveness of these drugs. Therefore it is still unknown whether the high-bolus dosage of tirofiban is safe and effective in patients undergoing primary PCI. The On-TIME 2 trial currently recruiting patients in the Netherlands and Germany will try to answer this question by measuring platelet function in patients with STEMI undergoing primary PCI randomised to high-bolus tirofiban or placebo.¹⁶ ■

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