Early double stent thrombosis associated with clopidogrel hyporesponsiveness

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Abstract A 57-year-old male patient without cardiovascular history suffered an acute myocardial infarction and underwent drug-eluting stent implantation in the left anterior descending artery. A few days later, the right coronary artery was also stented (drug-eluting stent). Three days later, he was re-admitted to our hospital in cardiogenic shock. Emergent coronary angiography showed total occlusion of both stents. Platelet function analysis (PFA) showed attenuated platelet inhibition in response to clopidogrel treatment. The patient was the carrier of a loss-of-function polymorphism in the *CYP2C19* gene, which has been associated with increased incidence of adverse thrombotic events. Antiplatelet therapy was switched to prasugrel and PFA revealed an adequate antiplatelet effect.

Keywords Thrombosis · Stents · Clopidogrel · Prasugrel · *CYP2C19*

Introduction

In patients undergoing percutaneous coronary intervention (PCI), dual antiplatelet treatment with aspirin and clopi-

dogrel is the therapy of choice for preventing thrombosis of the treated vessels [1]. Despite its proven benefit, inhibition of platelet function by clopidogrel treatment is characterised by large interindividual variability. It has been shown that hyporesponsiveness of platelets to clopidogrel therapy is an independent strong predictor of stent thrombosis [2, 3]. We report a case of simultaneous stent thrombosis in a patient with acute myocardial infarction who had an established clopidogrel hyporesponsiveness.

Case

A 57-year-old male patient without previous cardiovascular history suffered an acute myocardial infarction and underwent successful PCI of the culprit lesion in the right coronary artery (RCA) with implantation of a drug-eluting stent (DES, BioMatrix® 2.75×22mm). Before the PCI, the patient was anticoagulated (heparin 5000 IE) and loaded with antiplatelet agents (aspirin 320 mg and clopidogrel 600 mg) followed by aspirin 100 mg and clopidogrel 75 mg daily. One week later, elective PCI with DES implantation of a remaining lesion in the left anterior descending artery (LAD) was performed (Optima® 2.75×12mm).

Three days later, the patient developed severe chest pain and was re-admitted to our hospital in cardiogenic shock. The electrocardiogram (ECG) showed marked ST-segment elevation in leads II, III, and aVF, and V2-V5 (Fig. 1). Emergent coronary angiography (CAG) revealed occlusion of both stents (Fig. 2), which is classified as definite stent thrombosis according to Academic Research Consortium (ARC) criteria [4].

Intravenous administration of glycoprotein IIb/IIIa receptor blocker abciximab (bolus of 0.25 mg/kg of

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Fig. 1 ECG at re-admission showing marked ST-segment elevation in leads II, III, and aVF, and V2-V5

body weight followed by 0.125 $\mu\text{g/kg/min}$ continuous infusion for 12 h) was followed by balloon angioplasty, which resulted in Thrombolysis In Myocardial Infarction

(TIMI) III antegrade flow. Subsequently, the patient was sent to our cardiac high-care unit with the support of an intra-aorta balloon pump (IABP).

Fig. 2 Emergent coronary angiography at re-admission of (a) the right coronary artery (RCA) in the left anterior oblique view and (b) the left anterior descending artery (LAD) in the right anterior oblique view revealing occlusion of both stents (arrows). Balloon angioplasty resulted in thrombolysis in myocardial infarction (TIMI) III antegrade flow of the RCA (c) and the LAD (d)

Hirudin anticoagulated blood samples were taken during clopidogrel therapy and the remaining P2Y₁₂-mediated platelet aggregation was assessed by adenosine diphosphate and prostaglandin E1 (ADPtest HS)-induced platelet aggregation utilising multiple electrode (impedance) platelet aggregometry (MEA, Multiplate® analyser, Dynabyte, Munich, Germany) [5]. Aggregation was quantified on two separate days as area under the curve of arbitrary units (AU·minute). The MEA test revealed attenuated platelet inhibition during clopidogrel treatment (mean 47 AU·minute; target range for sufficient platelet inhibition <31 AU·minute). In addition, the patient was the carrier of the *CYP2C19**2 gene (LightMix®Kit, Tib MolBiol, Berlin, Germany).

Consequently, clopidogrel treatment was ceased and the patient was treated with prasugrel (60 mg loading dose followed by 10 mg daily). Platelet inhibition during prasugrel therapy was shown to be adequate (mean 23 AU·minute; target range <31 AU·minute). The patient recuperated well and was discharged several days later. He has been followed up at our outpatient department for over three months and remained free from symptoms.

Discussion

Dual antiplatelet treatment is advised for at least 12 months after DES implantation. The frequency of stent thrombosis is 1–2% despite dual antiplatelet treatment [6]. Early stent thrombosis (i.e., within 30 days) is mostly due to a mechanical complication whereas late stent thrombosis, especially in the DES era, is due to suboptimal endothelialisation. Several other factors, including undersizing or underexpansion, may contribute to early or late stent thrombosis. Recent data, however, show that an adequate antiplatelet effect is not achieved in 4% to 30% of patients receiving clopidogrel treatment [7, 8]. Thus, many patients may be resistant or only partially responsive to the antiplatelet effect of clopidogrel. Clopidogrel is an inactive pro-drug which is activated by the hepatic cytochrome P450 (CYP) system to generate its active thiol metabolite, which in turn irreversibly inhibits the ADP P2Y₁₂ receptor [9]. Hepatic metabolism of clopidogrel is achieved by a number of different hepatic CYP isoenzymes, including *CYP2C19*. The polymorphically expressed isoenzyme *CYP2C19* comprises a dominant part in this metabolism process [10, 11]. A loss-of-function polymorphism in the *CYP2C19* gene, known as the *CYP2C19**2 allelic variant, has been associated with increased levels of ADP-induced platelet aggregation in patients treated with clopidogrel. Besides the *CYP2C19**2 polymorphism, there may be other factors influencing the antiplatelet effect of clopidogrel including drug interaction

involving the cytochrome P450 enzyme, insulin resistance or poor bioavailability [12]. Consequently, a higher risk of adverse thrombotic events has been found after clopidogrel treatment [10, 13].

Prasugrel, a thienopyridine, possesses more rapid and greater inhibition of platelets. A recent clinical trial that used prasugrel in patients with acute coronary syndromes reported a 20% reduction in ischaemic endpoints and >50% reduction in the rate of stent thrombosis vs. patients receiving clopidogrel [14]. An increased risk for major bleeding was observed in the patients treated with prasugrel, however. A selective strategy of prescribing prasugrel only to patients harbouring reduced function alleles may magnify prasugrel's efficacy and limit the patients at risk for major bleeding.

There is increasing evidence that a tailored clopidogrel loading and maintenance dose according to platelet reactivity monitoring may decrease the rate of early stent thrombosis after PCI [15, 16]. Whether direct guidance of tailored antiplatelet therapy based on platelet function testing improves the clinical outcome of patients undergoing PCI remains unknown. Currently, the GRAVITAS (Gauging Responsiveness With A VerifyNow Assay-Impact On Thrombosis And Safety) trial [17] using a point-of-care assay is underway to address this issue in a large study population.

A future perspective may be genotyping for relevant polymorphisms in the hepatic CYP system. This could be performed before PCI and helps to identify a subpopulation of patients at high risk for stent thrombosis who could then be monitored by point-of-care platelet function tests for adequate response to clopidogrel.

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