CHOICE OF THERAPY FOR PATIENTS WITH REDUCED PLATELET INHIBITION AFTER CORONARY INTERVENTION

Hitesh Patel, Adeel Sahal, Roopen Arya, Ajay Shah and Rafal Dworakowski

ABSTRACT

Patients exhibiting inadequate response to anti-platelet therapy experience increased morbidity and mortality after percutaneous coronary intervention. Three different clinical cases are presented of patients with inadequate platelet inhibition, one of whom had a further cardiac event. Platelet inhibition was investigated using the VerifyNow P2Y12 test. High risk coronary intervention patients should have their platelet responsiveness checked. If an adequate response is not proven on standard therapy, then one of three strategies can be adopted: increased dosing of clopidogrel, clopidogrel switched to ticlodipine or clopidogrel switched to prasugrel.

Keywords: Platelet inhibition, stent occlusion

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INTRODUCTION

Anti-platelet agents have been a cornerstone in the management of coronary vascular disease especially after PCI where aspirin and clopidogrel are used in combination. Recent studies have shown that resistance to these agents is associated with significant patient mortality and morbidity.[1] Between 4 to 30% of patients treated with conventional doses of clopidogrel do not exhibit an adequate antiplatelet response.[2] There are currently no consensual guidelines for managing such patients. We report a series of cases of patient morbidity associated with clopidogrel resistance and a variety of solutions.

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CASE 1

A 60 year old lady who presented as an acute coronary syndrome (ACS) had percutaneous coronary intervention (PCI) with two drug-eluting stents (DES) to the left anterior descending coronary artery (LAD). 4 days post discharge on 75mg of aspirin and 75mg of clopidogrel (standard dose dual antiplatelet agents) she presented with a ST-segment elevation myocardial infarct. Coronary angiography and intravascular ultrasound (IVUS) demonstrated thrombotic occlusion of the LAD stent and a slightly under-deployed stent. After this was treated, a VerifyNow P2Y12 (validated blood test to assess thienopyridine platelet inhibition) showed only 11% inhibition (<10% poor inhibition, 10-50% fair inhibition, >50% good inhibition).[3] Her clopidogrel dose was increased to 300mg and a repeat VerifyNow improved to 26%.

CASE 2

A 78 year old man with extensive co-morbidities was admitted with troponin negative crescendo angina and found to have multi-vessel disease on coronary angiography. He had DES inserted into his left main coronary artery (LMS), left circumflex (LCx) and right coronary artery. He only had 4% platelet inhibition, which improved to 26% when his clopidogrel was changed to ticlodipine 250mg twice a day with no complications.

CASE 3

An 82 year old gentleman presented with ACS was found to have severe three vessel disease. He underwent IVUS-guided stenting of his LMS, LAD and LCx. Due to his extensive stenting and critical locations of his stent he had a Verify now test which showed 13% inhibition on standard anti-platelet agents. This was increased to 300mg clopidogrel but this still only maintained 13% inhibition. His Clopidogrel was changed to Prasugrel 5mg bd and he exhibited a 67% inhibition.

DISCUSSION

Platelet activation and aggregation play an important role in the pathogenesis of arterial thrombosis leading to ACS and in thrombotic complications after PCI. The thienopyridines, ticlopidine and clopidogrel, are agents that have been proven to be of benefit in the prevention of vascular ischemic events following PCI. Both drugs are prodrugs that, after hepatic biotransformation, inhibit ADP-induced platelet aggregation by specific blockade of the platelet P2Y<sub>12</sub> receptor.
Resistance to the action of clopidogrel may occur for several reasons, including drug under-dosing, impaired absorption, inefficient conversion of the pro-drug, drug-drug interactions that affect bioavailability or metabolism, and poor affinity of the active metabolite for the P2Y$_{12}$ receptor. Patients undergoing primary PCI with stenting who are resistant to clopidogrel have an increased risk of recurrent cardiovascular events.[4] Unfortunately, there is no agreement or consensus as to how to manage and treat patients hyporesponding to clopidogrel.

Higher loading doses and maintenance doses of clopidogrel have been shown to improve outcomes.[5] Switching to an alternative thienopyridine in this setting is one approach.[6] Long-term treatment with ticlopidine may cause neutropenia and thrombotic thrombocytopenic purpura. The recent introduction of prasugrel and the likely future availability of other novel agents (eg, cangrelora and AZD6140) may provide additional options. Prasugrel is a third generation thienopyridine that has been shown to be more effective than clopidogrel in reducing morbidity but has a slightly greater GI bleed rate.[7]

The VerifyNow P2Y12 assay measures platelet function by the rate and extent of light transmittance in whole blood as platelets aggregate over time in response to specific agonists. Low light transmittance reflects inhibited platelet function. The measurement correlates well to the gold standard and labour-intensive light transmittance aggregometry (LTA) for studying platelet reactivity.

In our practice, all patients that have early stent thrombosis have a VerifyNow test after IVUS and drug compliance checked. We also electively test platelet function pre-PCI in patients deemed to be at high risk of stent thrombosis. If reduced platelet inhibition is confirmed then we aim to optimise clinical factors by: addressing compliance with education and medication aids; reviewing drug interactions (e.g. replacing proton pump inhibitors); smoking cessation advice; and optimisation of glucose and cholesterol control. Based on the results of the VerifyNow test, potential strategies are to (1) Increase the dose of clopidogrel; (2) Switch clopidogrel to prasugrel; (3) Switch clopidogrel to ticlodipine – Table 1.

<table>
<thead>
<tr>
<th>VerifyNow (pre)</th>
<th>Intervention</th>
<th>VerifyNow (post)</th>
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<tbody>
<tr>
<td>Case 1</td>
<td>11%</td>
<td>Clopidogrel 300mg od</td>
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<tr>
<td>Case 2</td>
<td>4%</td>
<td>Ticlodipine 250mg bd</td>
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<tr>
<td>Case 3</td>
<td>13%</td>
<td>Prasugrel 5mg bd</td>
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Table 1: Summary of cases with VerifyNow results pre and post changes to anti-platelet agents
As near bedside platelet inhibition becomes more available, we hope larger scale studies are undertaken that will answer the question: what level of platelet inhibition is too low and merits a change in anti-platelet therapy.

REFERENCES


