Failure of high-dose clopidogrel in recurrent stent thrombosis

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ABSTRACT This case report describes recurrent drug-eluting stent thrombosis with documented laboratory hyporesponsiveness to clopidogrel. The use of escalating doses of clopidogrel prevented subsequent episodes, but the patient developed gastrointestinal intolerance and diffuse cutaneous reaction, which resolved completely with prasugrel. Impressively, prasugrel 10 mg daily achieved an even lower vasodilator-stimulated phosphoprotein platelet reactivity index compared to clopidogrel 300 mg daily. Our case highlights the importance of alternative P2Y12 receptor antagonists for patients receiving drug-eluting stents.

Keywords: clopidogrel, drug-eluting stent, P2Y12 receptor antagonists, prasugrel, thrombosis

INTRODUCTION

Dual anti-platelet therapy consisting of clopidogrel and aspirin is widely used to reduce the risk of thrombosis following coronary stent implantation. Despite this, up to 2% of elective cases and 6% of patients with acute coronary syndromes experience stent thrombosis,1,2 and this is partly attributed to hyporesponsiveness to clopidogrel.

High maintenance-dose clopidogrel (> 150 mg daily) and newer alternative drugs have both been proposed as measures to overcome poor response to standard maintenance-dose clopidogrel (75 mg daily).1,2 We describe the successful management of a patient with recurrent drug-eluting stent thrombosis and clopidogrel hyporesponsiveness who developed intolerance to high-dose clopidogrel.

CASE REPORT

A 53-year-old Malay man first presented with acute anterior ST-elevation myocardial infarction. He was given a loading dose of clopidogrel 600 mg and aspirin 300 mg before being transferred to the cardiac catheterisation laboratory for emergency angiography. It showed an isolated 100% obstruction of the mid-left anterior descending (LAD) coronary artery. After manual thrombectomy with a 6F Thrombuster II catheter, an 8.4 mg intracoronary bolus of abciximab was administered. Then the culprit segment was directly stented with a 3.0 mm × 18.0 mm Promus Element drug-eluting stent and post-dilatation was performed with a 3.25 mm × 15.0 mm NC Sprinter non-compliant balloon. The final angiogram confirmed good angiographic result with 0% residual stenosis and thrombolysis in myocardial infarction grade III antegrade flow without stent edge dissection.

On the same day after the angiography, the patient underwent a vasodilator-stimulated phosphoprotein (VASP) assay, which showed a platelet reactivity index (PRI) of 83.39% (Table I). His in-hospital recovery was uneventful and his discharge anti-platelet regimen comprised clopidogrel 75 mg and aspirin 100 mg daily (Table I). After 12 days, the patient was re-admitted with acute onset of central abdominal and chest pain. Electrocardiogram showed recurrent ST elevation in the anterior leads. He underwent emergency coronary angiography, which showed a 100% thrombotic occlusion of the previously stented segment. A 3.0 mm × 15.0 mm Sprinter legend balloon was deployed at low pressure within the LAD segment, followed by manual thrombectomy with a 7F Thrombuster II catheter. Intravascular ultrasonography (IVUS) study did not reveal under-expansion of stent from the first percutaneous coronary intervention (PCI) procedure. VASP assay showed a PRI of 70.76% (Table I). This was despite the fact that prior to the VASP assay, the patient had been compliant with his anti-platelet regimen of aspirin 100 mg and clopidogrel 75 mg daily. Thus, on his discharge, the dosage was increased to aspirin 100 mg and clopidogrel 150 mg daily (Table I).

After seven days, the patient was again admitted for left-sided chest pain. Electrocardiogram showed Q waves and deep T wave inversions in anterior leads. Emergency coronary angiography was performed, which again revealed 100% thrombotic occlusion of the LAD stent. Thrombectomy was used successfully for revascularisation. Repeat IVUS study did not reveal under-expansion of the stent to account for the episode. VASP assay showed a PRI of 73.94% (Table I), despite the patient’s compliance with his anti-platelet regimen of aspirin 100 mg and clopidogrel 150 mg prior to the VASP assay. The dosage was increased to aspirin 100 mg and clopidogrel 300 mg (Table I). The patient’s VASP assay showed a PRI of 42% (Table I) 11 days after starting the new dosage.
During an outpatient visit two months later, the patient complained of daily dyspepsia and a diffuse, non-pruritic rash (Fig. 1) that erupted after six weeks of treatment with clopidogrel 300 mg daily. He was therefore switched to prasugrel 10 mg daily (Table I). Within two weeks, the rash cleared completely and his dyspepsia resolved. A repeat VASP assay showed that the PRI had fallen to 37.05% (Table I). The patient remained symptom-free after 12 weeks of prasugrel treatment.

**DISCUSSION**

Increasing experience indicates significant variability in response to standard-dose clopidogrel and a diffuse, non-pruritic rash (Fig. 1) that erupted after six weeks of treatment with clopidogrel 300 mg daily. He was therefore switched to prasugrel 10 mg daily (Table I). Within two weeks, the rash cleared completely and his dyspepsia resolved. A repeat VASP assay showed that the PRI had fallen to 37.05% (Table I). The patient remained symptom-free after 12 weeks of prasugrel treatment.

**Table I. Anti-platelet, PRI and clinical progression of patient.**

<table>
<thead>
<tr>
<th>Day</th>
<th>Anti-platelet medicine (maintenance dose)</th>
<th>PRI (%)</th>
<th>Significant events</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-</td>
<td>83.39</td>
<td>Admitted for STEMI; underwent stenting with drug-eluting stent</td>
</tr>
<tr>
<td>5</td>
<td>Discharged with clopidogrel 75 mg and aspirin 100 mg daily</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>13</td>
<td>-</td>
<td>-</td>
<td>Admitted for recurrent STEMI caused by thrombotic occlusion of stent; underwent thrombosuction and revascularisation</td>
</tr>
<tr>
<td>14</td>
<td>-</td>
<td>70.76</td>
<td>-</td>
</tr>
<tr>
<td>16</td>
<td>Discharged with clopidogrel 150 mg and aspirin 100 mg daily</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>20</td>
<td>-</td>
<td>70.76</td>
<td>-</td>
</tr>
<tr>
<td>23</td>
<td>Discharged with clopidogrel 300 mg and aspirin 100 mg daily</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>34</td>
<td>-</td>
<td>42.14</td>
<td>-</td>
</tr>
<tr>
<td>76</td>
<td>-</td>
<td>-</td>
<td>Onset of diffuse, non-pruritic rash</td>
</tr>
<tr>
<td>80</td>
<td>Switched to prasugrel 10 mg and aspirin 100 mg daily</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

PRI: platelet reactivity index, STEMI: ST elevation myocardial infarction

also had greater risks of cardiovascular events, including stent thrombosis. In contrast, reduced-function CYP2C19 allele had no such influence on levels of active metabolites and platelet inhibition among people who took prasugrel. This presents CYP2C19 as a potential genetic marker that may help achieve effective anti-platelet therapy that caters to patients’ genetic differences.

Another test that may be used to optimise anti-platelet therapy is VASP. PRI-inhibition is linked to improved PCI outcome. Clopidogrel loading dose that was adjusted to optimise levels of PRI might improve clinical outcomes, including stent thrombosis after PCI,[5,6] even in patients with CYP2C19 loss-of-function allele, increasing clopidogrel loading dose could optimise PRI.[4] However, VASP assay is not routinely used. We need more evidence to prove that an individualised anti-platelet therapy guided by VASP can achieve greater efficacy with fewer side effects than the status quo.

Our patient’s PRI was eventually optimised with clopidogrel 300 mg daily, but he developed gastrointestinal symptoms and a diffuse cutaneous reaction. This alerts us to the limitations of clopidogrel and the importance of alternative drugs. Prasugrel was more effective in preventing ischaemic events than clopidogrel in patients with acute ST elevation myocardial infarction who undergo PCI.[9] Our patient’s improved clinical response after he switched to prasugrel shows that an individualised anti-platelet therapy, including the use of alternative drugs, can help improve outcomes.

In conclusion, this case suggests that double-dose clopidogrel is not suitable for every patient. The management of hypersensitivity is still an unresolved issue. Further studies are warranted to minimise thrombotic risk in patients receiving drug-eluting stents through individualised treatment strategies.
REFERENCES