Thienopyridines (ticlopidine and clopidogrel) are potent inhibitors of ADP-induced platelet aggregation (1-3). After metabolisation, the active metabolite irreversibly impairs the human platelet P2Y12 ADP receptor (3-7) and P2Y12 receptor-mediated inhibitory effect on prostaglandin E1-stimulated, cAMP-mediated phosphorylation of VASP (2, 4). In large clinical trials, clopidogrel or ticlopidine were shown to be superior to ASS in the prevention of vascular ischemic events (8). Clopidogrel plus aspirin is now standard therapy after the placement of coronary-artery stents to prevent stent thrombosis. Though clopidogrel was shown to be very effective for prevention of secondary atherothrombotic events in clinical trials, there are still patients who suffer vascular ischemic events despite treatment. Adverse cardiac events (cardiac death, myocardial infarction, revascularization) can be seen in 1.2-1.5% of patients under a 28-day combination therapy of clopidogrel and aspirin after stent placement (8). In addition to these clinical observations, studies investigating platelet inhibition after clopidogrel treatment have demonstrated individual variations in its anti-aggregating effects (9-12).

We report about a 64-year-old patient who was diagnosed with coronary artery disease, peripheral vascular disease, atrial fibrillation, arterial hypertension, hyperlipoproteinemia and nicotine abuse, and has a family history of coronary heart disease. In July 2003 the patient developed dyspnoea and angina pectoris. A coronary catheterization showed a stenosis in the left anterior descending coronary artery (LAD), after angioplasty a stent was implanted. The patient was released from the hospital in a stable condition. In February 2004 he was readmitted for recurrent angina pectoris. The coronary angiography showed an in-stent-stenosis; two Cypher stents were implanted. The medication was switched to ASS and clopidogrel. During his stay in the hospital the patient developed a urinary retention. Further investigation revealed a tumour in the bladder which required surgery. The patient was transferred to the department of urology. To minimize the perioperative bleeding complications it was planned to switch the anti-aggregatory medication from ASS and clopidogrel to tirofiban and the platelet function was monitored by aggregometry. Surprisingly, no clopidogrel-specific effect on ADP-induced platelet aggregation could be seen. A VASP (vasodilator-stimulated-phosphoprotein) phosphorylation assay (1, 2) revealed a clopidogrel non-responsiveness (Table 1). The medication was switched to ticlopidine 2 x 250 mg per day (+100 mg ASS). On day four of ticlopidine ingestion, the performed VASP assay showed a non-responsiveness to ticlopidine as well. During surgery no bleeding complications occurred. The medication was changed from ticlopidine to now 2 x 75 mg clopidogrel per day.

There is evidence that clopidogrel low responsiveness might influence the incidence of coronary stent thrombosis, as a strong correlation was found between clopidogrel effect and the occurrence of cardiovascular events (1, 11). Additionally, thienopyridines might have pleiotropic effects like decreasing the platelet-dependent mitogenesis of smooth muscle cells or CD 40L expression as possible mechanisms on the development of stent stenosis (13, 14). In former investigations, we found considerable differences in the responsiveness to clopidogrel and it was shown that 17.5% of the patients revealed a low-responsiveness to clopidogrel despite continuation of clopidogrel intake (10).

In the current case, the patient showed a low-responsiveness to clopidogrel as well as to ticlopidine. The platelet reactivity as measured by the P-VASP assay was 85 and 77% respectively. Platelet reactivity measured by the P-VASP assay should be decreased to under 50% in patients with normal responsiveness to thienopyridines (1, 2). Several questions arise from this case: what are predictors of acute or subacute stent thrombosis? What therapeutic manoeuvres should clinicians undertake when they encounter a patient with low responsiveness or even resistance to clopidogrel? In the current case a switch from clopidogrel to
ticlopidine was not effective, indicating identical mechanisms of drug resistance. Another approach to overcome low clopidogrel responsiveness could be an increase in clopidogrel dosage or to the use alternative anti-platelet agents such as CS-747 (LY640315) nonthienopyridine P2Y12 inhibitors such as AR-C69931MX, or antagonists of other platelet targets (15). Though acute stent thrombosis remains a rare clinical complication, some meta-analyses of coronary interventional studies addressed the question to identify predictors for acute or subacute stent thrombosis. Currently the initial coronary lesion length, the minimal lumen diameter within the stent and remaining local dissections are considered to be the most important factors predicting stent thrombosis. A recent publication (16) demonstrated that these local stent conditions cause stent thrombosis by showing luminal tissue protusion (identified by intravascular ultrasound) which highly correlated with this clinical complication.

Should platelet function routinely be measured in patients receiving thienopyridines? As variable thienopyridine responsiveness appears to be a common and important phenomenon with clinical relevance, only 1.5% of the patients after angioplasty develop complications. Therefore it might be beneficial to test the extent of thienopyridine effects under defined conditions with reliable and comparable methods; especially in patients receiving a Cypher stent with high risk for stent thrombosis. Although a specific test for this task (1 2, 10) is available, further investigations are necessary to determine its usefulness in clinical practice.

References


Table 1: Results of maximal ADP-induced platelet aggregation after clopidogrel, ticlopidine (in combination with aspirin) and tirofiban treatment. In the VASP assay, platelet reactivity should be under 50% in patients with normal responsiveness to thienopyridines.

<table>
<thead>
<tr>
<th>medication</th>
<th>platelet reactivity [%] VASP assay</th>
<th>max. aggregation [%] ADP-induced</th>
</tr>
</thead>
<tbody>
<tr>
<td>aspirin + clopidogrel</td>
<td>85.0</td>
<td>72.0</td>
</tr>
<tr>
<td>aspirin + ticlopidine</td>
<td>77.1</td>
<td>92.0</td>
</tr>
<tr>
<td>tirofiban</td>
<td></td>
<td>2.1</td>
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<tr>
<td>no medication</td>
<td>100</td>
<td>82.2</td>
</tr>
</tbody>
</table>