Repeated High Doses of Clopidogrel in 2 Cases of Pharmacological Resistance

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In the case of stent thrombosis and resistance to clopidogrel, choices of an alternative drug remain limited. In 2 cases of subacute stent thrombosis associated with clopidogrel resistance, an adequate response was obtained in these patients after repeated loading doses of clopidogrel. (*Circ J* 2008; 72: 2098–2100)

Key Words: Clopidogrel; Pharmacological resistance; Stent thrombosis

Acute stent thrombosis remains a dramatic complication of angioplasty and pharmacological resistance to clopidogrel can be involved in this phenomenon. In the case of stent thrombosis and resistance to clopidogrel, alternatives to clopidogrel remain limited. Recently, Aleil et al reported 3 cases of clinical and biological resistance to clopidogrel, despite overdosing to 150 mg of clopidogrel! Adequate inhibition of platelet activation was achieved with standard doses of ticlopidine, suggesting a different effect of these 2 molecules because of differences in pharmacokinetics and pharmacodynamics despite the same mechanism of action. We report 2 cases of subacute stent thrombosis associated with clopidogrel resistance.

Case Reports

Case 1

A 49-year-old man was admitted for acute coronary syndrome with troponin elevation. He had no history of systemic disease or cancer. His body mass index (BMI) was 25 kg/m². After a 300-mg loading dose of clopidogrel, the patient was administered a maintenance dose of 150 mg clopidogrel during the first month. Concomitant medications were aspirin, eptifibatide (a cyclic heptapeptide inhibitor of platelet GP IIb/IIIa), heparin, atorvastatin and atenolol. Coronary angiography revealed multivessel disease with normal left ventricular function. Percutaneous coronary intervention (PCI) was performed in 2 vessels, with 3 bare metal stents (BMS) in the left anterior descending (LAD) artery and 1 in the circumflex artery. Four days later, the patient presented a subacute stent thrombosis of the LAD, which was treated by urgent revascularization and tirofiban, a nonpeptide inhibitor of platelet GPIIb/IIIa.

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Analysis of VASP (VASP-FCM, Stago, Asnières, France) phosphorylation showed an inadequate response to clopidogrel, with a high platelet reactivity index (PRI of VASP) at 81%. A daily dose of 150 mg clopidogrel was administered and another 300 mg loading dose of clopidogrel. Despite this, the patient experienced another episode of subacute stent thrombosis on the following day. Urgent PCI enabled revascularization with new stent implantation because a local dissection was suspected. A new analysis of VASP revealed a persistent inadequate response with the PRI of VASP at 76%. We decided to administer another 600-mg loading dose, after which the PRI of VASP still remained high (71%), so we gave another 300-mg loading dose. After 18 days of treatment and a total of 3,150 mg of clopidogrel, the patient's PRI of VASP was 56% without recurrent stent thrombosis at follow-up and without hemorrhagic complications during hospitalization.

Case 2

A 48-year-old man was admitted for acute coronary syndrome. After a 300-mg loading dose of clopidogrel, the patient was administered a maintenance dose of 150 mg during the first month in addition to aspirin, heparin, atenolol, and atorvastatin. His BMI was 27 kg/m². Coronary angiography revealed 2-vessel disease involving the right and left circumflex arteries with normal left ventricular function. PCI was performed in the 2 vessels with 2 BMS, and there was a satisfactory angiographic result. Three days later, the patient presented a subacute stent thrombosis in the circumflex artery. Urgent PCI achieved revascularization with balloon angioplasty. Suspicion of clopidogrel resistance was confirmed with a PRI of VASP at 79% and with Verifynow P2Y12 (Accumetrics, San Diego, CA, USA) with only 6% inhibition (P2Y12 Reaction Unit (PRU)=363, BASELINE=387). A normal response to aspirin (Aspirin Reaction Unit=450) was observed with the Verifynow aspirin test. At 24 h after another loading dose of 600 mg clopidogrel, the PRI of VASP remained inadequate (72%). The Verifynow P2Y12 test showed 63% inhibition (PRU=132, BASELINE=357). We decided to give another 450-mg loading dose. After 1,800 mg of clopidogrel, the PRI of VASP was 49% and the Verifynow P2Y12 test revealed 67% inhibition (PRU=116, BASELINE=351) without recurrent stent thrombosis.

Discussion

Despite dual antiplatelet therapy, stent thrombosis remains a dramatic complication of stent implantation. Several local factors have been identified such as stent malposition, local dissection, and long and multiple stents. Resistance to antiplatelet agents has also been described.^{2,3}

There are several biological tests for evaluating the response to aspirin and clopidogrel. Response to clopidogrel can be assessed specifically with VASP phosphorylation, a test that has already been used to detect poor responders to clopidogrel with an increased risk of cardiovascular events.^{2,4} The Verifynow P2Y12 is a rapid point-of-care test that measures the level of platelet P2Y12 level blockade and it is well correlated with light transmittance aggregometry.⁵ It has been recently approved by the FDA for laboratory or point-of-care use to measure the platelet inhibition level in patients receiving clopidogrel.

Management of patients with recurrent subacute thrombosis remains an important challenge. Aleil et al describe 3 cases of stent thrombosis with clopidogrel resistance, despite overdosing to 150 mg of clopidogrel, so they replaced clopidogrel with a standard dose of ticlopidin and achieved an adequate biological response and absence of recurrence of thrombosis.¹

We report 2 cases of stent thrombosis with poor response to clopidogrel. A 48-year-old man had recurrent stent thrombosis with clopidogrel resistance. Pharmacoresistance to clopidogrel was demonstrated by the high level of the PRI of VASP phosphorylation. Despite a high maintenance dose of clopidogrel, biological and clinical resistance to clopidogrel occurred and a satisfactory response to clopidogrel, with a PRI of VASP = 56% and no recurrence of stent thrombosis, was only achieved with repeated loading doses of clopidogrel. In the second case, a poor response to clopidogrel was demonstrated by 2 different biological tests. After the initial loading dose of clopidogrel, VASP phosphorylation and Verifynow P2Y12 revealed an inadequate response. After a total dose of 1,800 mg clopidogrel, an adequate biological response was observed with VASP and Verifynow, without recurrence of coronary thrombosis or hemorrhagic complications.

Both of these patients presented with subacute stent thrombosis with a poor biological response to clopidogrel. Despite the initial loading dose and a 150-mg maintenance dose of clopidogrel, inadequate therapeutic response was clearly demonstrated by 2 different biological tests: VASP and Verifynow P2Y12. A satisfactory response was only achieved with repeated loading doses of clopidogrel.

Ticlopidin and clopidogrel have the same mechanism of action. Both are P2Y12 receptor antagonists and require metabolism with hepatic cytochrome P450 to be activated. The mechanisms leading to variability in clopidogrel responsiveness are multifactorial and may be related to reduced bioavailability of clopidogrel, such as non-compliance with therapy and drug interactions. Polymorphism of the receptor gene P2Y12^{6,7} cytochrome P4503A4⁸ and cytochrome P4502C19⁹ may also be involved. There is growing evidence that higher doses of clopidogrel may improve the response. In the ALBION study,¹⁰ a greater reduction of platelet activation with a dose–effect relationship was observed with high loading doses of clopidogrel (600 mg and 900 mg). In the case of pharmacoresistance to clopidogrel, we believe that repeated loading doses can be an alternative to ticlopidin, with fewer hematological side-effects. Adapting the doses of clopidogrel can be achieved with biological moni-

toring of antiplatelet agents, particularly in patients who develop stent thrombosis. We believe that repeated loading must be associated with overdosing of maintenance doses in cases of subacute stent thrombosis to complete the optimal range of platelet inhibition. An increase in bleeding complications associated with this high dose of clopidogrel is a potential concern. Nevertheless, to our knowledge, no hemorrhagic complications have been described in the 3 studies comparing 75 mg with 150 mg maintenance doses^{11–13} nor have they been described in studies comparing high loading doses of clopidogrel.^{10,14} Moreover, the analyses of bleeding events in the CHARISMA study¹⁵ suggest that patients with a high atherothrombotic risk are exposed to a lower risk of severe bleeding than patients with a low atherothrombotic risk. Hence, this management will probably need to be reconsidered soon with the advent of new antiplatelet agents such as Prasugrel and AZD6140 or Cangrelor.

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