Rapid oral desensitisation procedure in clopidogrel hypersensitivity

B. Oppedijk, D.A.M. Odekerken, J.J. van der Wildt, C.F. Melissant

We describe a patient who developed generalised pruritis with oedema and rash two weeks after she had started taking clopidogrel following coronary stent implantation. In the absence of other likely causative agents, clopidogrel hypersensitivity was probable. She was treated with a rapid oral desensitisation procedure, after which a daily dose of 75 mg clopidogrel was well tolerated. No major adverse events occurred during a follow-up period of eight months. Oral desensitisation in clopidogrel hypersensitivity seems to be a safe method to reduce the risk of coronary stent thrombosis. (*Neth Heart J* 2008;16:21-3).

Keywords: clopidogrel hypersensitivity, desensitisation, stent, thrombosis

Clopidogrel is a selective, irreversible inhibitor of adenosine diphosphate (ADP)-induced platelet aggregation for oral use. It is a pro-drug similar to ticlopidine, which requires activation by cytochrome P450-3A to become the active thiol derivative.

The combination of clopidogrel and aspirin is considered essential in reducing the risk of stent thrombosis in patients undergoing coronary stenting.¹ This risk seems to be higher in drug-eluting stents (DES) compared with bare-metal stents (BMS).^{2,3}

Several adverse drug reactions have been attributed to clopidogrel, varying from (urticarial) skin rashes to severe hypersensitivity syndrome with fever, neutropenia and pancytopenia.⁴⁻⁶ This can lead to early discontinuation of clopidogrel, and hence increase the risk of stent thrombosis.^{7,8}

In this study we describe a successful rapid oral desensitisation procedure in a patient who developed a probable case of clopidogrel hypersensitivity.

Case report

A 63-year-old female underwent a successful elective percutaneous coronary intervention (PCI) of the left anterior descending coronary artery (LAD) with placement of a drug-eluting stent (Taxus). She was prescribed clopidogrel for one year together with lifelong aspirin. Fourteen days after the PCI, while on holiday, she developed generalised pruritis together with oedema and a rash on her right hand. There were no signs of associated dyspnoea, wheezing or hypotension. She denied having been bitten by insects or any other alternative causes that on their own could have caused the reaction. Apart from the clopidogrel no other medication had been started recently. She consulted a local physician who, in collaboration with a university centre, diagnosed a hypersensitivity to clopidogrel. She was treated with an oral antihistamine and fractionated heparin 0.8 ml twice daily; the clopidogrel was discontinued. All symptoms gradually disappeared in approximately two weeks.

When she came to our outpatient clinic, we discussed the various treatment options with her as well as the risks and benefits of an oral desensitisation procedure. Informed consent was obtained for the latter. She was admitted to our coronary care unit where she was treated according to the protocol (table 1). The clopidogrel suspension was prepared as an extemporaneous formulation by our pharmacist (box 1). The procedure was uneventful. She was monitored overnight and could be discharged the next morning. In an eight-month follow-up period, a daily regimen of clopidogrel 75 mg was well tolerated.

B. Oppedijk

D.A.M. Odekerken

Department of Cardiology, Spaarne Hospital, Hoofddorp, the Netherlands

J.J. van der Wildt

Clinical Pharmacy, Spaarne Hospital, Hoofddorp, the Netherlands

C.F. Melissant

Department of Pulmonary Medicine, Spaarne Hospital, Hoofddorp, the Netherlands

Correspondence to: B. Oppedijk

Department of Cardiology, Spaarne Hospital, PO Box 770, 2130 AT Hoofddorp, the Netherlands

E-mail: boppedijk@spaarneziekenhuis.nl

Table 1. Clopidogrel desensitisation protocol.

Time (h)	Desensitising dose (mg)	Concentration	ml
0:00	0.005	0.5 mg/ml	0.01
0:30	0.010		0.02
1:00	0.020		0.04
1:30	0.040		0.08
2:00	0.080		0.16
2:30	0.160		0.32
3:00	0.30		0.60
3:30	0.60	5 mg/ml	1.20
4:00	1.20		0.24
4:30	2.50		0.5
5:00	5.0		1
5:30	10.0	75 mg tablet	2
6:00	20.0		4
6:30	40.0		8
7:00	75.0		1 tablet

All doses are given by mouth, each following dose after 30 minutes if no adverse reactions occur. Adapted from Camara MG et.al.¹³

Discussion

In our patient, the diagnosis of hypersensitivity to clopidogrel was made elsewhere. To be certain that clopidogrel was responsible for the hypersensitivity reaction, a re-challenge should be performed. We chose not to do so, because of the risk of serious adverse events as mentioned earlier. Using the Naranjo algorithm, a method for estimating the probability of adverse drug reactions, she scored 7 points, which makes clopidogrel a probable causative agent for the hypersensitivity reaction.⁹ This is confirmed by the World Health Organisation causality definitions, where the causality in this case was scored 'probable/likely'.¹⁰ In our opinion, there was no other option than to regard our patient as having clopidogrel hypersensitivity.

Alternative treatment options for clopidogrel are not readily available; substitute drugs are less effective or there is a potential cross-sensitivity. Ticlopidine has been withdrawn from the Dutch market because of its association with a higher risk of serious and potentially life-threatening adverse reactions compared with clopidogrel.¹¹ Fractionated heparin is not an alternative for platelet aggregation inhibitors.

There are, however, desensitisation protocols which have been published for several drugs, including a successful procedure for patients with aspirin hypersensitivity undergoing coronary stenting.¹² In general, the success rate of these protocols is between 70 and 90%. The approach is based on administering the drug at regular intervals, starting with a very low dose and escalating up to the therapeutic level while monitoring for symptoms of hypersensitivity.

Box 1.

Plavix® contains clopidogrel bisulphate which is not available as an active pharmaceutical ingredient. Clopidogrel is freely soluble in water; therefore, we used the Plavix® tablets. We crushed two tablets (150 mg) in a mortar to achieve a fine powder and added 5 ml of a base for suspension, which is a flavoured oral suspending vehicle. Adding 30 ml of this base resulted in a 5 mg/ml suspension (suspension 2). Then 1 ml of the suspension mentioned above (5 mg) was diluted up to 10 ml with the same base for suspension to obtain a suspension with a concentration of 0.5 mg/ml (suspension 1). There are no known data on the stability of clopidogrel in a solution (manufacturer's information). Therefore, the suspension should be prepared on the day of the procedure to minimise any possible loss of potency.

Until now, three reports on clopidogrel desensitisation have been published, comprising a total number of twelve patients.¹³⁻¹⁵ All patients developed pruritis and rash in a period of one day to three weeks after starting clopidogrel, the average being 6.5 days. Two patients also developed angio-oedema. In the reports, two different desensitisation protocols were used, the difference being the initial doses and dose escalation schedules. The procedure was well tolerated overall; rash occurred in two of the twelve patients during desensitisation. The next doubling dose was then delayed. Antihistamines and steroids were given, after which the regimen could be completed. For one patient a new protocol was developed with a lower starting dose and extended time intervals with good results. None of the patients developed anaphylaxis.

The precise mechanism of hypersensitivity to clopidogrel is not completely understood, but has been found to be IgE mediated.¹³ Contraindications for desensitisation are severe exfoliative dermatitis reactions such as Stevens-Johnson syndrome and toxic epidermal necrolysis (TEN).¹⁴ The effects of desensitisation can be temporary: if the drug is interrupted, it is possible that the patient recovers from the previous sensitivity within a few days. It is therefore wise to continue treatment in these patients once the desensitisation has been successful. There is currently no experience with repeated desensitisation to clopidogrel.

It is essential that the procedure is performed in a close-monitoring facility due to the possibility of serious adverse events. Preferably, antihistamines, β -blockers and steroids should be withdrawn three to four days before the procedure.

Conclusion

In clopidogrel hypersensitivity, a rapid oral desensitisation procedure seems to be a safe and successful method to reduce the risk of coronary stent

thrombosis. Although in our case a 100% causality was not established, our patient was able to continue clopidogrel on a daily regimen without any adverse effects and without having to be exposed to potentially serious adverse reactions as could be seen in a re-challenge. ■

References

- 1 Patrono C, Collier B, FitzGerald GA, Hirsh J, Roth G. Platelet-active drugs: the relationships among dose, effectiveness, and side effects: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. *Chest* 2004;**126**(suppl):234S-264S.
- 2 McFadden EP, Stabile E, Regar E, Cheneau E, Ong AT, Kinnaird T, et al. Late thrombosis in drug-eluting coronary stents after discontinuation of antiplatelet therapy. *Lancet* 2004;**364**:1519-21.
- 3 Ong AT, Hoye A, Aoki J, van Mieghem CA, Rodriguez Granillo GA, Sonnenschein K, et al. Thirty day incidence and six-month clinical outcome of thrombotic stent occlusion after bare-metal, sirolimus, or paclitaxel stent implantation. *J Am Coll Cardiol* 2005;**45**:947-53.
- 4 Gowda RM, Misra D, Khan IA. Hypersensitivity skin rash: an adverse drug reaction to clopidogrel loading dose. *Int J Cardiol* 2004;**95**:333.
- 5 Comert A, Akgun S, Civelek A, Kavala M, Sarigül S, Yildirim T, et al. Clopidogrel-induced hypersensitivity syndrome associated with febrile pancytopenia. *Int J Dermatol* 2005;**44**:882-4.
- 6 Doogue MP, Begg EJ, Bridgman P. Clopidogrel Hypersensitivity Syndrome With Rash, Fever, and Neutropenia. *Mayo Clin Proc* 2005;**80**:1386-70.
- 7 Ten Berg JM, van Werkum JW, Heestermans AACM, Jaarsma W, Hautvast RMA, den Heijer P, et al. Antiplatelet therapy in patients undergoing coronary stenting – the risk of late stent thrombosis. *Neth Heart J* 2006;**14**:297-300.
- 8 Van Werkum JW, Heestermans AACM, Jaarsma W, Hautvast RWM, de Boer MJ, ten Berg JM. Trombose van een coronaire stent na het staken van behandeling met clopidogrel. *Ned Tijdschr Geneesk* 2006;**150**:863-8.
- 9 Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts EA, et al. A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther* 1981;**30**:239-45.
- 10 World Health Organization: Adverse events following immunization (AEFI): causality assessment. <http://www.who.int/vaccines-documents/DocsPDF05/815.pdf>.
- 11 Szto GY, Linnemeier TJ, Ball MW. Fatal neutropenia and thrombocytopenia associated with ticlopidine after stenting. *Am J Cardiol* 1999;**83**:138-9.
- 12 Silberman S, Neukirch-Stoop C, Steg PG. Rapid desensitisation procedure for patients with aspirin hypersensitivity undergoing coronary stenting. *Am J Cardiol* 2005;**95**:509-10.
- 13 Camara MG, Almeda FQ. Clopidogrel (Plavix) desensitisation: a case series. *Cathet Cardiovasc Intervent* 2005;**65**:525-7.
- 14 Lee-Wong M, Gadhvi D, Resnick S. Clopidogrel desensitization. *Ann Allergy Asthma Immunol* 2006;**96**:756-7.
- 15 Walker NE, Fasano MB, Horwitz PA. Rapid Communication: Desensitization for the Management of Clopidogrel Hypersensitivity: Initial Clinical Experience. *J Invasive Cardiol* 2006;**18**:341-44.