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Desensitization to clopidogrel: a tailor-made protocol

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Summary
Clopidogrel is an antiplatelet drug widely used for treatment and prevention of a variety of cardiovascular diseases. We report a successful desensitization to clopidogrel in a 70-year-old Caucasian man with delayed hypersensitivity (HS) reaction. He developed lip, hand and foot swelling, erythematous papular non-pruritic lesions and arthralgias 2 weeks after starting treatment with clopidogrel 75 mg/d. A 3-hour desensitization protocol was started, achieving a cumulative dose of 154 mg without any reaction, and a daily dose of 75 mg was recommended. On the 4th day, the patient developed skin lesions similar to the previously described. He was treated with topical steroids and oral antihistamines, and the daily dose of clopidogrel was reduced to 20 mg. A new desensitization protocol was established, with a slow dose increment, according to the patient's response. It was only possible to achieve the dose of 75 mg/d after 2 months. Although well tolerated by most patients, HS reactions with clopidogrel may occur and desensitization is rising as a safe alternative in those patients. In delayed reactions with cutaneous lesions, a slower desensitization protocol may be necessary, as in this case.

Case Report

Clopidogrel is a thienopyridine antiplatelet drug widely used for treatment and secondary prevention of a variety of cardiovascular diseases (1). Its combination with acetylsalicylic acid is considered essential to reduce the risk of stent thrombosis in patients undergoing coronary stenting (2). Although clopidogrel is well tolerated in the majority of patients, mucocutaneous reactions have been described: fixed drug eruption (1), oral erosive lichen planus (3), hemorrhagic herpes zoster (4), maculopapular pruritic skin rashes (5) and angioedema (1). The alternative thienopyridine, ticlopidine, is more expensive and associated with serious side effects, such as neutropenia, thrombotic thrombocytopenic purpura, bone marrow aplasia and renal failure, limiting its clinical safety and utility (6). Clopidogrel is, therefore, the preferred thienopyridine in all cases. When hypersensitivity reactions occur, as other treatment options are limited and frequently not tolerated, desensitization is rising as a safe alternative (7). Drug desensitization is defined as the induction of a temporary state of tolerance to a compound responsible for a hypersensitivity reaction, which can only be maintained by continuous administration of the drug (8). If the drug involved is discontinued, tolerance is lost within a period of time that can vary from a few hours to a few days (8). In this procedure, increasing doses of the drug are administered over a short period of time until the total cumulative therapeutic dose is achieved and tolerated (8).

We report a successful desensitization to clopidogrel in a patient with delayed hypersensitivity reaction.

A 70-year-old Caucasian man with allergic rhinitis, hypertension, dyslipidemia and chronic gastritis was submitted to coronary catheterization with placement of a stent and prescribed clopidogrel 75 mg/day. Longstanding medication included ramipril, carvedilol, nitrates, indapamide, acetylsalicylic acid

Table 1 *- Desensitization protocols to clopidogrel*

	Day	Time (min)	Concentration	Dose (mg)	Cumulative Dose (mg)
1st protocol	1	00	**0.5 mg/mL**	0.05	0.05
		20		0.1	0.15
		40		0.5	0.65
		60	**5 mg/mL**	1.0	1.65
		80		2.5	4.15
		100		5	9.15
		120		10	19.15
		140		20	39.15
		160		40	79.15
		180	**75 mg**	75	154.15
	2-8		**75 mg**	75	
	Day	**Time (days)**	**Concentration**	**Dose (mg)**	
2nd protocol	9-15	7	**5 mg/mL**	20	
	16-18	3		30	
	19-41	23		40	
	42-44	3		45	
	45-50	6		50	
	51-53	3		55	
	54-56	3		60	
	57-59	3		65	
	60-63	4		70	
	64		**75**	75	

and simvastatin. Two weeks after starting treatment with clopidogrel, he developed lip, hand and foot swelling, erythematous papular non-pruritic lesions on the neck and abdomen, and arthralgias. He was admitted at the emergency department, treated with oral deflazacort and hydroxyzine, and clopidogrel was stopped. Laboratory evaluation, which included complete blood count, erythrocyte sedimentation rate, immunoglobulins (G, A, M and E), rheumatoid factor and antinuclear antibodies revealed no abnormalities. Cutaneous lesions resolved in five days and arthralgias in three weeks. He was referred to our outpatient clinic for suspected drug allergy. Patch tests with different concentrations of clopidogrel (10%, 30% and 50% pet) and oral challenge (cumulative dose of 75 mg) were negative. One week later, the patient started continuous administration of the drug and 24 hours after a single dose he developed erythematous papular pruritic lesions. Skin biopsy suggested drug related dermatitis: epidermis with multifocal mild spongiosis, exocytosis of lymphocytes and rare vacuolar degeneration of the basal layer, multifocal dermal edema, perivascular inflammatory infiltrate of lymphocytes and rare eosinophils, and macrophages. He was advised to avoid clopidogrel and treatment with ticlopidine was started but it was not well tolerated due to gastrointestinal symptoms. Since dual antiplatelet therapy was required and therapeutic alternatives to clopidogrel are limited, a three-hour desensitization protocol was started, achieving a cumulative dose of 154 mg (**table 1**, 1st protocol) without any reactions. A daily dose of 75 mg was recommended. On the 4th day, the patient developed skin lesions similar to the previously described. The daily dose of 75 mg was continued for 4 more days, with simultaneous treatment with topical mometasone and oral rupatadine. Due to persistence of skin lesions, the dose of clopidogrel was reduced to 20 mg/day, and maintained for

7 days. A new desensitization protocol was established, with a slow dose increment, according to the patient's response (**table 1**, 2nd protocol). Clopidogrel administration was performed at home and the patient was evaluated in our outpatient department every 3 days, or less if the clinical situation warranted earlier evaluation. During the 2nd protocol, when skin lesions reappeared they were treated with topical corticosteroids and oral antihistamines previously used, and clopidogrel dose was increased only when there was a marked improvement of skin lesions. The dose of 75 mg/day was only achieved after two months. Even though clopidogrel was well tolerated, the patient decided to stop its administration one month later. This means that he did not understand the principle of drug desensitization, which was explained several times and it was included in the written informed consent. The case was discussed with the cardiothoracic surgeon and given the patient's non-compliance it was decided not to start a new desensitization procedure.

Although well tolerated by most patients, hypersensitivity reactions with clopidogrel may occur. Since other treatment options are limited and frequently not tolerated, desensitization is an alternative in patients who require prolonged dual antiplatelet therapy. Some protocols for desensitization to clopidogrel have been published, demonstrating its safety and effectiveness (6,7,9,10).

Cutaneous hypersensitivity reactions to drugs may be caused by different pathogenic mechanisms. Despite negative patch tests to clopidogrel, the authors consider that a specific involvement of T cells may be suggested by histological findings on skin biopsy of dermal perivascular inflammatory infiltrate with lymphocytes and scarce eosinophils and macrophages.

According to a recent publication of the European Drug Allergy Interest Group there is no universal or consensus drug desensitization protocol for delayed-type hypersensitivity reactions, and protocols vary in duration, ranging from a few hours to several weeks. Patients with delayed reactions may benefit from longer protocols, with repetitive and slowly increasing doses, since rush protocols frequently have a higher failure rate (11).

The authors present a tailored-made desensitization protocol to clopidogrel that can be used in an outpatient setting. This case also highlights the importance of patient awareness for the need of continuous drug administration so that tolerance can be maintained.

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