

CASE REPORT

CASO CLINICO

Clopidogrel as a safe alternative in patients with urticaria and angioedema induced by ticlopidine: a case report

Il clopidogrel può essere una valida alternativa in pazienti con sindrome orticaria-angioedema causata dall'utilizzo di ticlopidina: descrizione di un caso clinico

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Parole chiave

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Summary

A 58-year-old man with coronary stent implantation showed urticaria and angioedema after the beginning of ticlopidine therapy. The temporal relationship between the use of ticlopidine and urticaria-angioedema and the absence of other possible causes of urticaria, let us to suspect an adverse reaction to ticlopidine. Owing to the necessity to prevent stent thrombosis, the patient was submitted to challenge-test for clopidogrel without adverse reaction. Although ticlopidine and clopidogrel are structurally similar and are metabolised by the same hepatic enzymes, the two drugs do not share any common metabolite. Thus, we hypothesize that the mechanism of the adverse reaction differs for the two thienopyridine derivatives depending on the different compounds derived from metabolism.

In conclusion, physicians should be aware that clopidogrel may be a suitable alternative in patients with adverse reaction to ticlopidine.

Riassunto

Un uomo di 58 anni con stent coronarico, manifestava orticaria-angioedema subito dopo trattamento con ticlopidina. La relazione temporale tra l'uso della ticlopidina e la comparsa di orticaria-angioedema avvalorava il sospetto di una reazione avversa al farmaco. Data la necessità di prevenire una possibile complicanza trombotica, il paziente veniva sottoposto a challenge-test con clopidogrel senza che si evidenziasse alcuna reazione avversa. Sebbene ticlopidina e clopidogrel siano strutturalmente simili e vengano metabolizzati dagli stessi enzimi epatici, è noto che i due farmaci non hanno metaboliti comuni. Questo fa ipotizzare che il meccanismo delle reazioni avverse dipenda dai diversi metaboliti dei due derivati tienopiridinici. In conclusione, nei pazienti con reazione avversa a ticlopidina, il clopidogrel può essere una valida alternativa.

Introduction

Ticlopidine and clopidogrel are thienopyridine derivatives widely used as platelet aggregation inhibitors in preventing cardiovascular events in cerebrovascular, cardiovascular and peripheral vascular diseases¹.

The two drugs have a very similar chemical structure, clopidogrel differing for the presence of a carboxymethyl side group only². Both drugs share the same pharmacological activity, inhibiting the binding of adenosine 5'-diphosphate to its platelet receptor P2Y₁₂³ and are metabolized by the hepatic cytochrome P450-1A enzyme system with the production of different metabolites.

Despite its effectiveness, ticlopidine is associated with a significant incidence of severe side effects. Also, clopidogrel, occasionally provokes urticaria and angioedema⁴.

We report a case of successful use of clopidogrel in a patient with ticlopidine-induced severe urticaria-angioedema.

Case report

A 58-year-old man was admitted to our Division for generalized urticaria and eyelid angioedema. His medical history included hypertension, hyperchole-

sterolemia, NID diabetes and coronary heart disease. Longstanding medications included aspirin, furosemide, ramipril, carvedilol, simvastatin, metformin hydrochloride, esomeprazole. Moreover, the patient initiated therapy with ticlopidine to prevent stent thrombosis after coronary stent implantation. After some days, he showed a widespread urticarial reaction and severe eyelid oedema, treated with a methylprednisolone bolus (1 g) and antihistamines. Symptoms resolved over a week after ticlopidine therapy was discontinued and a tapering dose of corticosteroid was started.

To find possible causes of urticaria, during hospitalization, the patient underwent several laboratory examinations. RAST for common inhalant and food allergens was negative. Liver and kidney function tests, platelet count, C3, C4, C1 inhibitor, CPK, CK-MB, LDH and troponine serum levels, and stool examination for parasites were within the normal range or negative. In light of these findings, we suspected an adverse reaction to ticlopidine.

Two weeks after the complete regression of skin manifestations, the patient was submitted to challenge-test with clopidogrel. The test was performed with increasing doses of the drug, according to the guidelines of the Italian Society of Allergy and Clinical Immunology. The patient tolerated the drug and a treatment with clopidogrel was started. No adverse reaction has been observed in a six months follow-up.

Discussion

It is known that ticlopidine may cause allergic or pseudoallergic reactions, such as urticaria, itch, ma-

culopapular eruption or fixed drug eruption⁵. The hypothesis of adverse reaction to ticlopidine in our patient was supported by a temporal relationship between the use of this drug and the manifestation of urticaria-angioedema and by the absence of other identified causative factors. The performance of the challenge-test to clopidogrel was suggested by the need to prevent stent thrombosis and from the knowledge that clopidogrel has a more favorable side-effect profile than ticlopidine. Although ticlopidine and clopidogrel are structurally similar and are metabolized by the same hepatic enzymes, it is known that the two drugs do not share common metabolite⁶. Clopidogrel, in fact, undergoes rapid hydrolysis into a carboxylic acid derivative (SR 26334)⁷, the main circulating metabolite that has no effect on platelet aggregation. The active metabolite of clopidogrel, instead, is a highly unstable compound that in vitro exhibited all the biological activities of clopidogrel observed *ex vivo*, even if only one metabolite of the 8 isomers exhibits in vitro antiplatelet activity. Whether this compound is the sole active metabolite of clopidogrel remains to be elucidated, but it is clear that this molecule is different from that formed from ticlopidine^{8,9}. In fact, in a recent study in the rat, the molecule responsible for the in vivo activities of ticlopidine, called UR-4501, was identified among in vitro metabolites¹⁰.

In the light of these findings we hypothesize that the mechanism of the adverse reaction differs for the two thienopyridine derivatives depending on the different profile of metabolites.

In conclusion, in patients with adverse reaction to ticlopidine, physicians should be aware that clopidogrel may be a suitable alternative.

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