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Delayed hypersensitivity to new oral anticoagulants. Demonstration of cross reactivity for the drug category and definition of non-irritant concentrations for patch tests

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Summary
The current therapy with direct trombin inhibitors (DTI) is indicated for the prevention of stroke in non-valvular atrial fibrillation. Side effects are reported, particularly skin hypersensitivity, for this whole category of drugs as well as for other modern antiplatelet and anticoagulant drugs.
For their clinical features, these reactions appear as delayed T-cell mediated drug hypersensitivity, but at present there are no diagnostic methods of investigation. We reported a case of delayed skin reaction to edoxaban and we found the non-irritant concentration for patch test in the whole category of drugs.
The patch test resulted positive for edoxaban. A successive challenge with alternative DTIs and/or a switch to warfarin is proposed as alternative therapy.

Introduction

The new oral anticoagulants, Direct Thrombin Inhibitors (DTIs) or Non-vitamin K Oral AntiCoagulants (NOACs) are a class of anticoagulant drugs indicated for the prevention of strokes and systemic embolism in non-valvular atrial fibrillation (1). This class of anticoagulant drugs has a direct effect on the Factor X of the coagulation cascade, and doesn't require the use of antithrombin as mediator. In Italy there are four molecules approved by the Italian Drug Agency (AIFA): rivaroxaban, apixaban, edoxaban, dabigatran. Dabigatran acts selectively by inhibiting thrombin. Edoxaban is a direct inhibitor of factor Xa. The clinical use of these drugs is similar to the use of the dated vitamin K antagonists (warfarin and acenocoumarol, also called AVK), which actually have an effect on different levels of the coagulation cascade, acting on the synthesis of various coagulation factors (II, VII, IX, X) in the liver.
According to the ESC guidelines (European Society of Cardiology), non-vitamin K oral anticoagulants (NOACs) are indicated for patients: (2) with non-valvular atrial fibrillation (FANV) lasting ≥ 48h, or when the duration of atrial fibrillation is unknown. Oral anticoagulant treatment (e.g. vitamin K antagonists with INR 2-3 or NOACs) is recommended for ≥ 3 weeks before and for ≥ 4 weeks after cardioversion.
In patients with risk factors for stroke or recurrent atrial fibrillation (FANV), oral anticoagulant treatment, either with AVK (INR 2-3) or new oral anticoagulants, should be continued chronically, regardless of the apparent maintenance of sinus rhythm after cardioversion.

Post-marketing observations have shown side effects (3) for the whole category of these drugs, especially skin hypersensitivity. Dermatitis have been reported, with varying frequency: for edoxaban, a skin reaction is an adverse effect reported as common. Rivaroxaban (4-13) has shown a similar dermatitis frequency; as for apixaban, the reaction is uncommon (14), while it is rare in the case of dabigatran (15-19) (**figure 1**).
These reactions appear for their clinical feature as a delayed T-cell mediated drug hypersensitivity, but at present there are no diagnostic methods of investigation.
For this reason, we report a clinical case demonstration of the presence of T-cell mediated sensitization caused by these drugs; given this case, we propose a diagnostic protocol and choice of alternative NAOs.

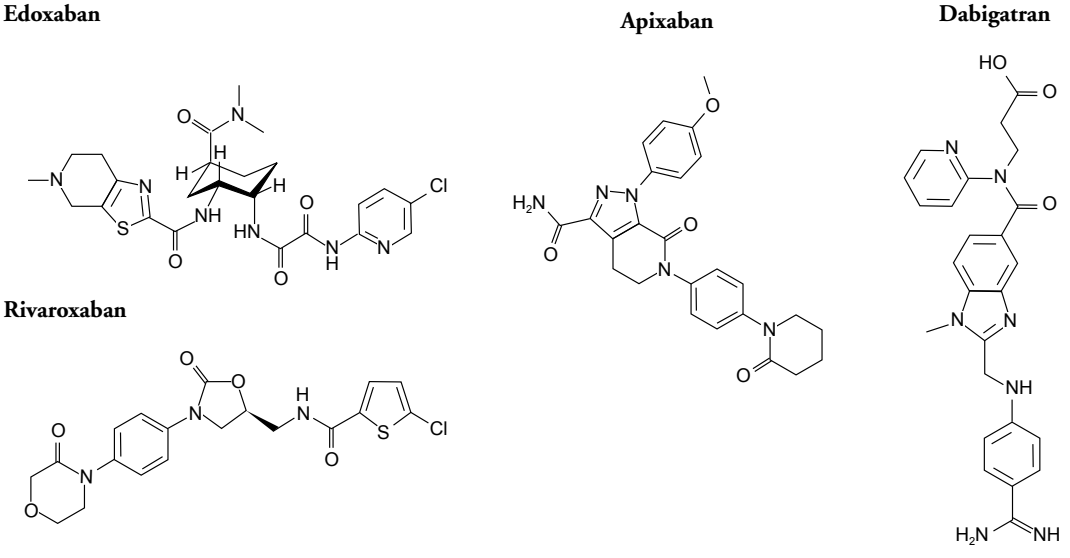
Clinical case

The patient is a seventy-year-old woman discharged from department of Internal Medicine with the following diagnosis: heart failure in atrial fibrillation; hypertensive heart disease with hypokinetic-dilatative evolution and mitral valvular prolapse, aneurysm of the interventricular septum. The patient has been treated with: furosemide 25 mg, kanrenoatus 2 mg, ramipril 5 mg, bisoprolol 2.5 mg, allopurinol 150 mg, enoxaparin 8000 IU 1 fl sc twice a day. During the recovery the patient has started therapy with edoxaban, 60 mg 1 cp daily.
Objectively, the patient appeared to be dyspneic even after mild efforts, and presented malleolar oedema. Ten days after the start of the edoxaban therapy, she showed symptoms of prurigo and widespread erythematous lesions. These lesions were attributed to edoxaban, for which the skin reaction is an adverse effect reported as common. Therefore, the patient underwent an allergological examination and skin tests for calciparin, enoxaparin, nadroparin, which resulted negative.
Consequently, the treatment with edoxaban was suspended, while the treatment with enoxaparin alone was continued. The symptoms gradually resolved at home. The possible adverse reaction to edoxaban as "culprit drug" was reported to the Internal Pharmacy.
Considering the available data about possible adverse reactions, the drug to be preferred seemed to be dabigatran.

Material and methods

A galenic preparation was set up in the Hospital Pharmacy: rivaroxaban-Xarelto®, 20 mg whole tablets crushed in a mortar and mixed with vaseline at 10% and 30%; the same preparation was adopted for: dabigatran-Pradaxa® 150 mg tablets, at 10 and 30% vaseline; apixaban-eliquis® 5 mg tablets at 10 and 30% vaseline; edoxaban-Lixiana® 60 mg tablets at 10 and 30% vaseline.
Six healthy controls tested negative with identical preparation. The patch was negative at 72 h, but after five days it tested positive for dabigatran-pradaxa® at 10% +, and at 30% ++, and for edoxaban-Lixiana® + at 30%. The patient then performed a gradual challenge procedure with apixaban-eliquis® (negative patch test) 2.5 mg on the first day, tolerated, then after 24 h in two administrations, tolerated as well. Unluckily, the drug

Figure 1 *- Chemical structure of direct trombin inhibitors.*



was tolerated only for seven days; after that, symptoms of widespread eczematous dermatitis started to appear again.
Hence the administration of apixaban was halted, and the patient was treated with an antihistamine and oral steroid; subsequently she showed remission of symptoms in seven days; she underwent simultaneous reintroduction of enoxaparin.
The following cardiological choice was to switch to an oral anticoagulant therapy with warfarin, which was finally tolerated by the patient.

Discussion

The new oral anticoagulants present relatively common skin reactions according to post-marketing surveillance data. The most common reactions are of the erythematous eczematous type. On the other hand, various and more serious clinical features are reported in literature: leukocytoclastic vasculitis, drug induced hypersensitivity syndrome (DIHS) (7), drug induced drug reaction with eosinophilia and systemic symptoms (DRESS) (8).
Eczematous dermatitis seems to be caused by T cells mediated immune reaction. The patch test is therefore an appropriate method for the diagnosis of such reactions. The exposed case highlights for the first time the presence of a specific T-cells delayed type hypersensitivity to these drugs. The concentration of such drugs crushed as whole tablets in a mortar and mixed in vaseline at 30% appears to be non-irritant on the tested healthy subjects and can be used for diagnosis. An even more delayed reading of the test, after a few days, appears significant. We also established the non-irritant concentration for patch test and we suggest a late lecture of the test at five days. The presence of allergic cross reactivity among the category of drugs is also demonstrated.
The challenge with a new alternative oral anticoagulant or the switch therapy to warfarin may be the subsequent therapeutic choice.

Conflict of interest

The authors declare that they have no conflict of interest.

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