Allergy to Rivaroxaban Cross-Reactivity with other Direct Anticoagulants and the Role of the Basophil Activations Test: A Case Report

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Direct- acting oral anticoagulants (DOACs) are used to prevent stroke and systemic embolism in predisposed patients. They are increasingly used owing to their benefits over other anticoagulants such as warfarin and acenocoumarol. DOACs are considered safer and do not need frequent monitoring through regular blood tests, dosage adjustments, or perioperative specific management [1]. These drugs have been reported to induce immediate hypersensitivity reactions (HSRs), mainly cutaneous reactions (e.g. urticaria, angioedema, lichenoid reaction) and, very rarely, anaphylaxis (0.01% of reported cases) and delayed HSR [2-8]. Furthermore cross-reactivity between DOACs has been reported [1,9-10]. However, to date, the underlying immune mechanism responsible for these reactions has not been fully elucidated because of a lack of data from allergy studies. The case we present is the first reported instance of an IgE-mediated reaction to rivaroxaban with a positive basophil activation test (BAT) result, after an anaphylactic reaction.

A 72-year-old man, without history of interest, was referred to our allergy clinic after presenting with a pruriginous exanthematous rash that initially affected the **outer ears**, before progressing to the face and trunk. The reaction occurred during the night, almost 12 hours after (althougt the patient was sleeping), the first time he took rivaroxaban and enoxaparin sodic (this which was later tolerated at home) after being diagnosed with atrial

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fibrillation. The patient also complained of dizziness without loss of consciousness during the episode, which self-resolved in a few minutes. During the allergy workup, prick-prick testing with rivaroxaban was negative. No other tests were performed in the absence of previous scientific evidence. Given the patient's need to maintain this treatment owing to previous poor control with other anticoagulants and under the request of his Hematologist, a controlled oral dose escalation challenge at our clinic was proposed. After signing the consent form, a total dose of 20 mg of rivaroxaban was administered. Three hours after the last dose, he developed pruritus affecting the pinnae and a pruriginous exanthematous rash affecting the face and trunk. He gradually developed nausea, dizziness, pallor, and hypotension. He was treated rapidly with 0.3 mg intramuscular epinephrine, 40 mg, intravenous (IV) methylprednisolone, 100 mg, IV hydrocortisone, 5 mg, IV dexchlorpheniramine, and IV fluids. His condition resolved, and he was asymptomatic after 2 hours.

A blood test performed at the time showed neutrophilia and elevated tryptase (15.7 ng/L; cut-off 12 ng/L).

After the challenge, an IgE- mediated reaction was suspected, and a BAT was performed with the culprit drug and other DOACs in order to find a safe alternative. Rivaroxaban, apixaban, and edoxaban yielded positive results, and dabigatran, a negative result (Table 1). Therefore, a challenge with dabigatran was proposed. After signing the informed consent form, the patient tolerated an oral dose escalation challenge, reaching a total dose of dabigatran of 110 mg. The patient continued to take this dose at home, with no further complications.

Rivaroxaban, is a new oral anticoagulant that reversibly inhibits factor Xa. DOACS are increasingly prescribed. Physicians should be aware of potential HSRs.

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Several cases of mild cutaneous reactions have been published, as have cases of anaphylaxis and severe cutaneous adverse reactions, such as drug reaction with eosinophilia and systemic symptoms, acute generalized exanthematous pustulosis, and Stevens-Johnson syndrome [2-6].

However, to date, the HSRs reported have been diagnosed solely on the basis of the clinical history and timeline, with no allergology workup demonstrating the immune mechanism underlying the reactions. Using the Naranjo algorithm, our patient exhibited a definite probability of HSR to rivaroxaban (10 points). In addition, in the case we report, the positive BAT result and the elevated tryptase level during the reaction, together with the clinical history, confirmed an IgE-mediated reaction to rivaroxaban.

Cross-reactivity in DOACs assessed based on clinical findings has been reported between apixaban and rivaroxaban [10] and between rivaroxaban and dabigatran [1,9].

According to the BAT results, we found a possible cross-reactivity between rivaroxaban, apixaban, and edoxaban, which are all coagulation factor X and Xa blockers, respectively. However, dabigatran, a direct thrombin inhibitor with a slightly different structure compared with the other DOACs, did not produce a positive result, postulating as a safe alternative that was confirmed later with an oral controlled test.

Of note, the dizziness reported by the patient during the first reaction was not considered related to the adverse drug reaction at the first evaluation. Onset of the reaction the first time he took the drug and resolution of the symptoms without medication or further complications, acted as cofounders, thus preventing us from suspecting an IgE-mediated reaction. The outcome of this case highlights the relevance of considering all symptoms that appear during adverse reactions, even if they do not seem related.

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Taken together, these data suggest that personalized evaluation of adverse reactions to DOACs should be performed. In addition, the use of *in vitro* diagnostic tests even if they are not standardized for the suspect drug, can be useful in the allergy workup.

Although we believe that prescription of DOACs is safe, increasing use has led to a rise in the frequency of HSRs, including anaphylaxis. No standardized approach has been established with respect to symptoms during adverse reactions, allergy diagnostic tools, and targeted management.

We describe the first case of confirmed IgE-mediated HRS due to rivaroxaban based on a positive BAT result and elevated tryptase during the reaction. We also show possible cross-reactivity between DOACs that can be effectively assessed using the BAT to identify a potentially safe and effective treatment alternative.

CONFLICTS OF INTEREST

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