

Allergy to Rivaroxaban: A Case Report Showing Cross-Reactivity With Other Direct Anticoagulants and the Role of the Basophil Activation Test

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J Investig Allergol Clin Immunol 2023; Vol. 33(5): 405-406
doi: 10.18176/jiaci.0883

Key words: Rivaroxaban. Allergy to direct anticoagulants. Basophil activation test.

Palabras clave: Rivaroxaban. Alergia a anticoagulantes directos. Test de activación de basófilos.

Direct-acting oral anticoagulants (DOACs) 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 specific perioperative management [1]. However, they have been reported to induce immediate hypersensitivity reactions (HSRs), mainly cutaneous reactions (eg, urticaria, angioedema, lichenoid reaction) and, very rarely, anaphylaxis (0.01% of reported cases) and delayed HSRs [2-8]. Furthermore, cross-reactivity between DOACs has been reported [1,9-10]. 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 anaphylactic reaction to rivaroxaban with a positive basophil activation test (BAT) result.

A 72-year-old man with no 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 while the patient was sleeping, almost 12 hours after his first dose of rivaroxaban and enoxaparin sodium for atrial fibrillation. He later tolerated enoxaparin sodium at home. The patient also complained of dizziness without loss of consciousness during the episode, which self-resolved in a few minutes. During the allergy work-up, 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 at the request of his hematologist, a controlled oral dose escalation challenge at our clinic was proposed. After signing the consent form, the patient received a total dose of 20 mg of rivaroxaban. Three hours after the last dose, the patient reported 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 intramuscular

Table. Basophil Activation Tests Results.^a

Drug	% CD63+ basophils	Stimulation index	Result
Rivaroxaban	7.6	5.6	Positive
Apixaban	22	16.3	Positive
Edoxaban	24	17.7	Positive
Dabigatran	0.8	–	Negative

^aValues ≥ 2 are considered positive for direct oral anticoagulants

epinephrine 0.3 mg, intravenous (IV) methylprednisolone 40 mg, IV hydrocortisone 100 mg, IV dexchlorpheniramine 5 mg, 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). 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. Physicians should be aware of potential HSRs, since DOACs are increasingly prescribed.

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 based on the clinical history and timeline, with no allergology work-up demonstrating the immune mechanism underlying the reactions. According to the Naranjo algorithm, the patient exhibited definite probability of HSR to rivaroxaban (10 points). In addition, an IgE-mediated reaction to rivaroxaban was confirmed by the positive BAT result and the elevated tryptase level during the reaction, together with the clinical history.

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

The BAT results indicated possible cross-reactivity between rivaroxaban, apixaban, and edoxaban, which are all coagulation factor X and Xa blockers. However, dabigatran, a direct thrombin inhibitor whose structure differs slightly from that of other DOACs, did not produce a positive result, thus making it a safe alternative, as subsequently confirmed in a controlled oral challenge test.

Of note, the dizziness reported by the patient during the first reaction was not considered related to the adverse drug reaction in 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 the symptoms that appear during adverse reactions, even if they do not seem related.

Taken together, these data point to the need for personalized evaluation of adverse reactions to DOACs. In addition, *in vitro* diagnostic tests can prove useful in the allergy workup, even if they are not standardized for the suspect drug.

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, or targeted management.

We report the first case of confirmed IgE-mediated HSRs due to rivaroxaban based on a positive BAT result and elevated tryptase levels 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.

Funding

The authors declare that no funding was received for the present study.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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■ *Manuscript received October 17, 2022; accepted for publication December 19, 2022.*

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