



Letters

Delayed hypersensitivity reactions to edoxaban

Edoxaban is the fourth approved direct oral anticoagulant (DOAC) that has been introduced in the European market (2015), after dabigatran (2008), rivaroxaban (2008), and apixaban (2011). Dabigatran is the only direct thrombin inhibitor, whereas apixaban, edoxaban, and rivaroxaban are factor-Xa inhibitors. In a few years, DOAC use has steadily increased in clinical practice for the prevention of stroke and systemic embolism in adult patients with nonvalvular atrial fibrillation (NVAf)¹ and for the treatment and prevention of recurrent deep vein thrombosis and pulmonary embolism.²

A better safety profile, ease of monitoring, and probable non-inferior therapeutic effectiveness have led to increased use of DOACs in many countries. Although hemorrhage-related adverse reactions of DOACs have been well characterized, nonhemorrhage-related adverse effects have been reported, which considerably complicates management of these patients. Although drug hypersensitivity reactions (DHRs) are relatively uncommon, it is important to consider that clinicians may prefer to maintain patients on a different DOAC as opposed to switching to warfarin and may need guidance from an allergist on how to proceed. Several case reports of DHR to dabigatran, rivaroxaban, and apixaban³ have been published, but to our knowledge, only a few cases of delayed hypersensitivity to edoxaban have been described in the literature thus far.^{4,5} We report 3 cases of suspected DHR to edoxaban referred to our clinic in the previous 5 months.

To give consistency and collect all relevant available information, a standardized questionnaire developed by the European Network for Drug Allergy⁶ was used as a guide and recommended algorithms for causality assessment, that is, the World Health Organization–Uppsala Monitoring Centre causality assessment system⁷ and the Naranjo Adverse Drug Reaction Probability Scale⁸ were applied.

A 70-year-old White man, with a medical history of cardiac amyloidosis and smoldering myeloma, was hospitalized for worsening dyspnea and fever. At admission, antibiotic therapy (clarithromycin) was started and edoxaban was prescribed for the treatment of newly diagnosed NVAf. The patient's home medications were continued (furosemide, atorvastatin, and tamsulosin). After 5 days, he developed a pruritic, maculopapular exanthema on the trunk and lower limbs. Routine laboratory test results were within normal ranges, including complete blood cell count, erythrocyte sedimentation rate, and serum beta 2 microglobulin, whereas the qualitative Bence-Jones protein test result was negative. Clarithromycin was stopped, edoxaban was replaced with fondaparinux, and systemic corticosteroids and antihistamines were given for 4 to 5 days with complete resolution of the skin lesions. Upon discharge, the patient was instructed to start

anticoagulation therapy with warfarin in addition to all the other home medications and was referred for further allergy evaluation. After 1 month of discharge, the patient had completed a 7-day course of clarithromycin for a new upper airway infection without any adverse reaction. Furthermore, he lamented significant difficulty in maintaining therapeutic international normalized ratio values. Graded challenge test with rivaroxaban (drug indicated by cardiologist) was performed and well tolerated. The patient is still taking the drug.

A 73-year-old White woman with a suspected hypersensitivity to edoxaban was referred to our unit. Her past medical history included ischemic stroke in NVAf in 2016, acute myocardial infarction in 2010, hypertension, and type 2 diabetes mellitus. For 3 years, her home medications included aspirin, metoprolol, furosemide, insulin, and dabigatran. At a follow-up cardiological visit, dabigatran was replaced with edoxaban because of renal failure (creatinine clearance, 20 mL/min). After 10 days of starting edoxaban, the patient developed a raised, pruritic, maculopapular rash involving the trunk and proximal extremities; the severity was mild to moderate. Edoxaban therapy was stopped and topical corticosteroid treatment was prescribed, with complete resolution within 2 weeks. Given the fragility of the patient, no challenge test with an alternative DOAC was performed, and warfarin was prescribed by the cardiologist for anticoagulation.

A 60-year-old man with a 7-year history of NVAf treated with rivaroxaban was referred to our unit. However, 6 months previously, he had temporarily stopped rivaroxaban for selective orthopedic surgery. Approximately 1 week after restarting the drug, he developed a pruritic rash, and the cardiologist replaced rivaroxaban with edoxaban, without a substantial clinical improvement. At the time of our visit, the patient presented with a diffuse, pruritic maculopapular rash, more pronounced on the trunk, and facial erythema. Laboratory test results, including autoantibodies (ie, antinuclear, antidouble-stranded DNA, anti-extractable nuclear antigen antibodies), were all within normal ranges. The clinical course was favorable, with progressive resolution of exanthema 2 weeks after the initiation of corticosteroids and discontinuation of edoxaban therapy. Approximately 2 weeks later, a graded challenge test with an alternative DOAC (apixaban) was performed and tolerated. The patient is still taking the drug.

In these patients, the clinical features, timing between the start of therapy and the onset of reaction (7–15 days), and resolution of the rash upon discontinuation of edoxaban treatment are strongly compatible with a delayed-type DHR.⁹ Applying both causality scales (the World Health Organization–Uppsala Monitoring Centre and the Naranjo scale), a causal relationship between taking edoxaban and the adverse cutaneous reaction resulted “probable” in all 3 cases.

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Drug provocation test with the suspected culprit was not considered appropriate or clinically necessary in these patients. Switching to another alternative DOAC was possible (patients 1 and 3), even if cross-reactivity might have occurred (patient 3). Given the rarity of cases and the lack of evidence, it is not currently possible to better define cross-reactions and preferential switches at the moment. Nevertheless, a diagnostic algorithm, including patch testing, for DHR to DOAC has been previously proposed.^{3,5}

In conclusion, the aforementioned described suspected DHR to edoxaban presented the following similar hallmarks to those of other DOACs, as reported in the literature and in our experience⁵: most frequently, delayed-type reactions, particularly T-cell mediated, and mild to moderate in severity.

These 3 cases highlight the importance of raising clinicians' awareness on the risk of immune-mediated reactions to edoxaban, which might still be underestimated. Patch tests may be used in the future to evaluate alternative DOACs and to guide subsequent oral drug tolerance tests in patients with mild delayed hypersensitivity reactions.

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