

## Case in Point

# Medication-Induced Pruritus From Direct Oral Anticoagulants

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Prescribing an antihistamine that is taken at the time of the anticoagulant dose may allow patients with possible direct oral anticoagulant-associated pruritus to continue therapy.

**P**runitus is a subjective report of itching, which can be caused by dermatologic or systemic conditions. Pruritus accounts for about 5% of all skin adverse drug reactions (ADRs) after administration.<sup>1</sup> Mechanisms by which medication-induced pruritus occurs are still unknown and have been understudied. Treatment modalities also have been understudied; however, the understood method for treatment is cessation of the causative agent.<sup>2</sup>

Anticoagulants commonly are used in several conditions, including prevention of ischemic cerebrovascular accident (CVA) in patients with atrial fibrillation (AF) as well as for the treatment and prevention of deep vein thrombosis (DVT) and pulmonary embolism (PE).<sup>3</sup> Traditionally, warfarin was the gold standard anticoagulant. With the relatively recent approval of several direct oral anticoagulants (DOACs), such as rivaroxaban, apixaban, and dabigatran, the landscape of antico-

agulation is changing. One benefit of using DOACs as opposed to warfarin is that they often require less frequent laboratory monitoring. However, rare ADRs not detected during clinical trials have appeared following drug approval.<sup>4</sup>

In a VA anticoagulation clinic that managed more than 60 patients taking DOACs, the authors identified 2 cases of pruritus, possibly associated with DOAC agents. These 2 cases point to a higher incidence rate than the rate reported in the rivaroxaban package insert (2%).<sup>5</sup> Of note, pruritus is not mentioned in the apixaban package insert.<sup>6</sup>

### **PATIENT 1 CASE PRESENTATION**

Patient 1 was a 69-year-old male with AF who was switched to rivaroxaban after 5 years of warfarin therapy. Past medical history included iron deficiency anemia, hypertension, type 2 diabetes mellitus, systolic heart failure, hyperlipidemia, hepatic steatosis, benign prostatic hyperplasia, and gastroesophageal reflux disease. The patient reported “itching all over” soon after initiation of rivaroxaban and that the itching was intolerable and always began 90 to 120 minutes after each dose of rivaroxaban with no associated rash.

After about 6 months of treatment with rivaroxaban, the patient was switched to apixaban; however, the pruritus persisted even after the switch. The onset of itching had similar timing with regard to the apixaban doses. When apixaban was initiated, the patient also was started on amiodarone and tamsulosin. A full pharmacotherapy review of the patient’s medication list for the incidence of pruritus was conducted. Regarding amiodarone and tamsulosin, incidence of pruritus was < 1%.<sup>7,8</sup> Neither agent had yet been started during the rivaroxaban therapy; therefore, it was unlikely that either of these 2 medications were the causative agent of the pruritic ADR.

In response to the itching, the patient was given diphenhydramine 25 mg twice daily, taken with each dose of apixaban. Shortly thereafter, the patient reported that diphenhydramine lessened the severity of the pruritus. He was switched to loratadine 10 mg twice daily with each dose of apixaban, to avoid drowsiness as well as the increased anticholinergic ADRs of first-generation antihistamines. The patient reported that the itching was tolerable.

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## PATIENT 2 CASE PRESENTATION

Patient 2 was a 63-year-old male with AF and hypertension who was initially started on rivaroxaban and reported pruritus after about 1 month. Despite the uncomfortable itch, the patient elected to continue therapy and began diphenhydramine 25 mg daily with each dose of rivaroxaban. Diphenhydramine seemed to improve the pruritus but did not completely alleviate it. While on rivaroxaban, the patient experienced an acute drop in hemoglobin; however, no source of bleeding was found. Although the pruritus was largely resolved, he was switched to apixaban due to its favorable bleeding profile.<sup>9</sup> The patient continued to have pruritus on apixaban; however, he reported that pruritus was less severe than it had been while taking rivaroxaban. The patient restarted on diphenhydramine twice daily with each dose of apixaban and reported cessation of pruritus.

## DISCUSSION

After observing both cases in relation to the timing between the administration of a DOAC and onset of pruritus, it seemed likely that the causative agent could be the DOAC. A Naranjo Nomogram was used to determine the likeliness of each

drug to be the causative agent of the ADR.<sup>10</sup> This nomogram is scaled from a low score of -4 to a high score of 13. Patients 1 and 2 had a score of 4, which is reflective of a possible ADR (score 1-4). Using the nomogram as well as the subjective information provided by the patients, it is reasonable to conclude that the pruritus was possibly associated with the use of the DOACs. Nonadherence to anticoagulants may lead to potentially fatal adverse outcomes, such as stroke. Medication-associated pruritus could lead to medication nonadherence if left unaddressed. It is notable that prescribing an antihistamine that is taken at the time of the anticoagulant dose allowed these patients with possible DOAC-associated pruritus to continue therapy with the selected anticoagulant. Further research on this topic is needed. ●

### Author disclosures

*The authors report no actual or potential conflicts of interest with regard to this article.*

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## REFERENCES

1. Reich A, Ständer S, Szepletowski C. Drug-induced pruritus: a review. *Acta Derm Venereol.* 2009;89(3):236-244.
2. Ebata T. Drug-induced itch management. *Curr Probl Dermatol.* 2016;50:155-163.
3. Burnett AE, Mahan CE, Vazquez SR, Oertel LB, Garcia DA, Ansell J. Guidance for the practical management of the direct oral anticoagulants (DOACs) in VTE treatment. *J Thromb Thrombolysis.* 2016;41(1):206-232.
4. U.S. Department of Health and Human Services, U.S. Food & Drug Administration. FDA Adverse Events Reporting System (FAERS) public dashboard. Apixaban. <https://fis.fda.gov/sense/app/777e9f4d-0cf8-448e-8068-f564c31baa25/sheet/45beeb74-30ab-46be-8267-5756582633b4/state/analysis>. Updated August 31, 2017. Accessed November 8, 2017.
5. Xarelto [package insert]. Titusville, NJ: Janssen Pharmaceuticals Inc; 2011.
6. Eliquis [package insert]. Princeton, NJ: Bristol-Myers Squibb Company; New York, NY: Pfizer Inc; 2016.
7. Pacerone [package insert]. Minneapolis, MN: Upsher-Smith Laboratories Inc; 2008. Minneapolis, MN.
8. Flomax [package insert]. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals Inc; 2016.
9. Granger CB, Alexander JH, McMurray JJ, et al; ARISTOTLE Committees and Investigators. Apixaban versus warfarin in patient with atrial fibrillation. *N Engl J Med.* 2011;365(11):981-992.
10. Michel DJ, Knodel LC. Comparison of three algorithms used to evaluate adverse drug reactions. *Am J Hosp Pharm.* 1986;43(7):1709-1714.



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