

Dronedarone-induced photoallergic reaction



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Key words: dronedarone; Multaq; photoallergic reaction; spongiotic dermatitis.

INTRODUCTION

Photosensitivity is the broad term used to denote adverse reactions to light. These 2 main reactions are phototoxic and photoallergic. Dronedarone is a noniodinated benzofuran derivative. It is structurally similar to and shares the antiarrhythmic properties of amiodarone, and thus it is used in the treatment of paroxysmal or persistent atrial fibrillation and atrial flutter.¹ The pulmonary and thyroid toxicities associated with amiodarone have not been observed with dronedarone. Systemic side effects associated with dronedarone range from common gastrointestinal distress (eg, nausea, vomiting, and diarrhea) to severe liver injury and hepatic failure. While toxic epidermal necrolysis has been reported, cutaneous reactions appear to be an uncommon side effect of dronedarone therapy and have been generally nonspecific.²⁻⁵ Across 5 clinical studies (n = 6285), cutaneous adverse reactions (ie, eczema, pruritus, allergic dermatitis, or any other nonspecific rash) occurred in <5% of dronedarone versus 3% of placebo patients; <1% were photosensitivity reactions.⁶

The authors present a 67-year-old female who demonstrated dronedarone associated photoallergic drug eruption that resolved within 2 weeks post medication cessation. Differentiating features of phototoxic and photoallergic reactions are also briefly discussed.

CASE REPORT

A 67-year-old Caucasian woman with a history of atrial fibrillation presented to the clinic complaining of pruritic reddish discoloration of her anterior lower portion of the neck, upper portion of the chest, and dorsal aspects of both the forearms (left > right) after



Fig 1. The patient's left forearm depicting the erythematous plaques. Proximal and distal biopsy specimens were obtained.

significant sun exposure for the week prior to presentation. The patient started dronedarone 400 mg twice daily 1 month prior to presentation. Her past medical history was significant for hypertension, hyperlipidemia, hypothyroidism, lichen sclerosus, and osteoarthritis. The patient's other medications included 0.1% triamcinolone acetone topical cream, aspirin 81 mg, levothyroxine 150 mcg, lisinopril 5 mg, lorazepam 0.5 mg, metformin 500 mg, rosuvastatin 20 mg, nitroglycerin 0.4 mg, rivaroxaban 2.5 mg, vitamin D3, vitamin B12, and folate. The patient denied any known drug allergies and any associated symptoms including worsening arthritis, dyspnea, or mouth ulcers.

Physical examination revealed confluent erythematous papules coalescing into plaques over the lower anterior aspect of the neck, upper portion of the chest, and bilateral forearms (Fig 1). There was

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Funding sources: None.

Conflicts of interest: None disclosed.

IRB approval status: Not applicable.

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JAAD Case Reports 2020;6:1208-10.

2352-5126

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<https://doi.org/10.1016/j.jdcr.2020.10.003>

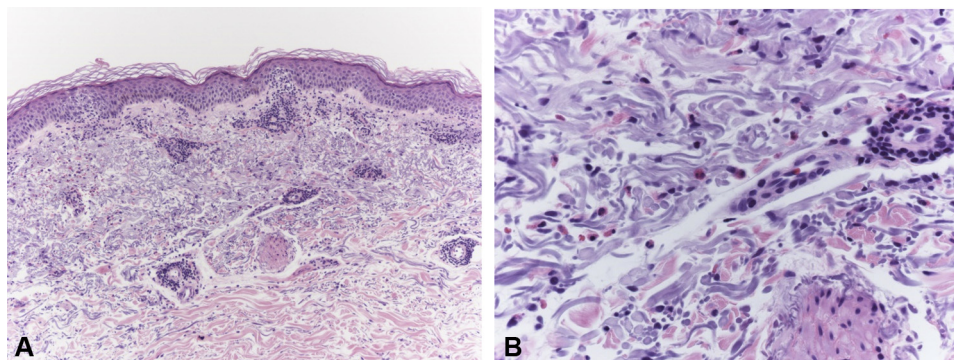


Fig 2. **A**, Left distal forearm: superficial to mid-dermal perivascular dermatitis with eosinophils and mild spongiosis. **B**, Left proximal forearm: perivascular lymphocytic inflammation with scattered interstitial eosinophils. (**A** and **B**, stain; original magnifications: **A**, $\times 10$; **B**, $\times 20$, hematoxylin and eosin stain).

a notable sparing of the submental region, abdomen, and legs. Laboratory tests, including complete blood count and comprehensive metabolic panel, were within normal limits. All serologic titers (ie, antinuclear antibody, anti-Ro/SSA, anti-La/SSB, and anti-Smith antibodies) were negative.

The two biopsies showed a superficial- to mid-dermal perivascular predominantly lymphocytic dermatitis, with scattered interstitial eosinophils and mild, focal epidermal spongiosis (Fig 2). A periodic acid–Schiff stain was negative for fungi. There was no histologic evidence of connective tissue disease. The most probable diagnosis of photoallergic reaction to dronedarone was made based on the clinical presentation and clinical pathologic correlation. Dronedarone was discontinued, and the patient was prescribed 0.05% betamethasone dipropionate topical ointment to help control the eruption and associated pruritus. Her rash completely resolved within the subsequent 2 weeks.

DISCUSSION

Medications causing photodrug reactions include the following therapeutic classes: antibiotics, antihistamines, diuretics, antiarrhythmics, antidiabetics, nonsteroidal anti-inflammatory drugs, and psychiatric medications, among others.⁷ Drug photosensitivity to exogenous agents can induce phototoxicity and photoallergy. Phototoxic reactions are mediated mainly by free radicals, causing cell damage by cell membrane injury in an oxygen-dependent process.

Photoallergic drug reaction is a type IV hypersensitivity response (ie, delayed or cell-mediated), which requires specific sensitization to a

photoactivated drug. Photoallergic reaction can be produced by substances that are applied topically or taken systemically and, in contrast to phototoxic reactions, it does not depend on the concentration of the photosensitizer. However, many photosensitive drugs can cause both photoallergic and phototoxic reactions.⁸

The clinical features of photoallergic reactions can closely resemble an eczematous reaction, such as in contact dermatitis, and usually occur days to weeks after starting the medication and subsequent sun exposure.⁹ The terminal elimination half-life of dronedarone varies from 13 to 31 hours.¹ Thus, patients should refrain from sun exposure for at least 5-9 days post medication cessation. Our patient noticed the initial onset of the eruption 3 weeks after starting dronedarone, which progressed over the next 1 week. This timeline is similar to the dronedarone photodermatitis described in literature (Table 1).^{2,3,5} However, except for the study by Al-Jarrah et al, which benefits from photopatch data,¹⁰ the diagnosis was not specifically characterized in previously reported cases, potentially due to the lack of histopathology. It is possible that based on the clinical presentation, those patients may have had a similar photoallergic reaction.

CONCLUSION

Dronedarone is a benzofuran analog of amiodarone, for which photoallergy needs to be considered by dermatologists and cardiologists if their patients present with a photodistributed

Table I. Reported cases of patients presenting with a photodistributed eruption post recently starting dronedarone, 400 mg twice daily

Publications	Age/Gender	Onset	Duration	Treatment	Histology/Photopatch
This study	67/Female	3 weeks	2 weeks	Drug cessation 0.05% betamethasone dipropionate topical ointment	Histology: Perivascular lymphocytic infiltrate with eosinophils and epidermal spongiosis
Al-Jarrah et al, 2020 ¹⁰	64/Female	4 weeks	3-4 weeks	Drug cessation steroid ointment and antihistamine	Photopatch testing with dronedarone "as is" was positive (++) 2 and 3 days after irradiation with 5 J/cm ² ultraviolet A
Datar et al, 2019 ³	70/Female	4 weeks	2 weeks	Drug cessation	Not performed
Lee et al, 2017 ¹¹	56/Male	4 weeks	1 week	Drug cessation systemic steroid, antihistamine, and topical corticosteroid	Photopatch: Positive reactions were recorded only to dronedarone at the site exposed to ultraviolet A
Kuo et al, 2014 ²	61/Female	4 weeks	2 weeks	Drug cessation 0.05% fluocinonide ointment and oral hydroxyzine	Not performed
Ladizinski et al, 2013 ⁵	63/Female	Recent	5 days	Broad-spectrum sunscreens 0.1% betamethasone valerate cream	Not performed

eruption. Patients need to be monitored and advised optimal photoprotection if dronedarone is initiated.

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