Facial Hyperpigmentation Caused by Diltiazem Hydrochloride

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Diltiazem hydrochloride, a member of the calcium channel blocker family of antihypertensive medications, has been found to produce many cutaneous reactions, such as photodistributed hyperpigmentation. We report a 53-year-old black woman who presented with facial darkening that began 6 months after starting diltiazem. Areas were not responsive to topical bleaching creams. Biopsy showed postinflammatory pigment alteration with a largely burned-out lichenoid dermatitis. The results of all laboratory evaluations were negative, including complete blood cell count, antinuclear antibodies, anti-Ro antibodies, and anti-La antibodies. Patch testing and photo-patch testing to numerous drugs including diltiazem were negative. Phototesting revealed a normal minimal erythema dose to UVA but a slightly reduced minimal erythema dose to UVB. Diltiazem was then stopped and hydralazine hydrochloride was started. While UVA has been thought to be the main culprit in drug-induced photosensitive reactions, this case demonstrates that UVB may possibly play a role in diltiazem-induced photodistributed hyperpigmentation.

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Case Report

A 53-year-old black woman (Fitzpatrick skin type V) presented with progressive darkening of the face, concentrated around the eyes, of 6 months' duration. Based on a differential diagnosis that included melasma or postinflammatory hyperpigmentation, she was treated with hydroquinone cream 4% and a broad-spectrum sunscreen for 4 months with minimal improvement. She then started to develop dark patches on her temples and cheeks; all areas became progressively worse and were unresponsive to hydroquinone. She reported mild pruritus. Her medical history was remarkable for hypertension, type 2 diabetes mellitus, asthma, and arthritis.

The patient started taking diltiazem hydrochloride 6 months prior to presentation for discoloration of the face. Other medications included metformin for 10 years, glipizide for 14 years, and rosiglitazone maleate for 5 years.

On physical examination, the patient had dark brown, hyperpigmented, reticulated patches around the eyes and on her temples and cheeks (Figure 1). Histopathologic examination revealed postinflammatory pigment alteration with a strong representation of a largely burned-out lichenoid dermatitis.

Laboratory evaluations included complete blood cell count, antinuclear antibodies, anti-Ro antibodies (Sjögren syndrome antigen A [SS-A]), and anti-La antibodies (Sjögren syndrome antigen B [SS-B]), which were all negative. The patient underwent patch testing to the North American Contact Dermatitis Group series and no relevant allergens were detected.[1] Photo-patch testing to the North American Contact Dermatitis Group phototray and diltiazem also were negative. She also underwent phototesting with UVA and UVB and was found to have no reaction to 10 J/cm^2 of UVA but a slightly reduced minimal erythema dose to UVB of 160 mJ/cm^2 (reference range for Fitzpatrick skin type V, 205–520 mJ/cm^2).[2] Diltiazem was then stopped and hydralazine hydrochloride was started. Approximately 6 months after diltiazem was stopped, the patient was noted to have considerable improvement without the use of additional topical bleaching agents (Figure 2).

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The authors report no conflict of interest.

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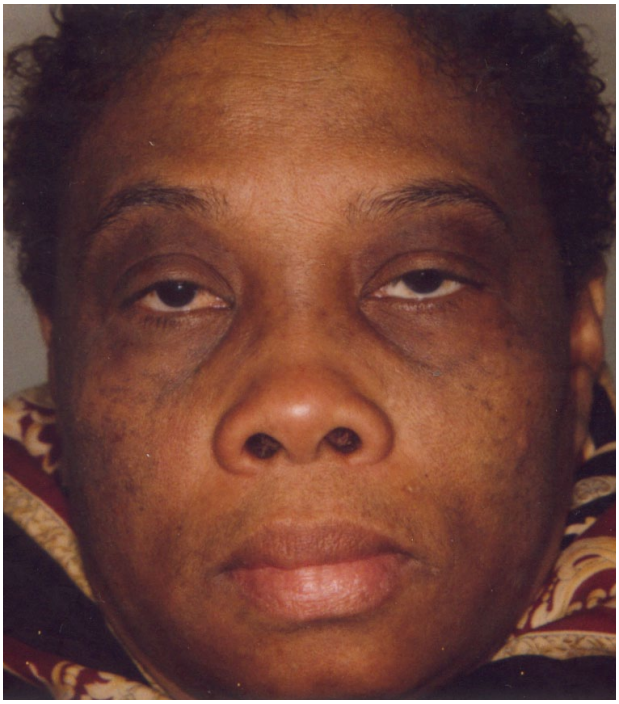

Figure 1. Photodistributed hyperpigmentation.

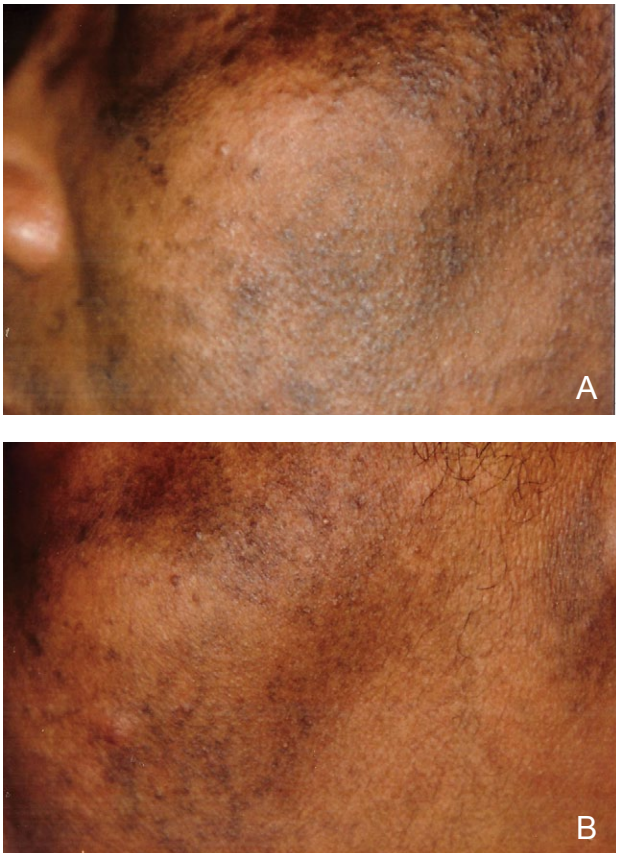

Figure 2. Facial hyperpigmentation 2 months after initial presentation prior to stopping diltiazem hydrochloride therapy (A) and 6 months after stopping diltiazem and adding hydralazine hydrochloride (B).

Comment

Diltiazem, a calcium channel blocker, is a potent vasodilator commonly used in the treatment of hypertension, angina, and other cardiac issues.[3] Cutaneous side effects to diltiazem can comprise up to 48% of the side effects of this medication, as reported by Knowles et al,[4] including drug hypersensitivity syndrome, pruritic exanthematous eruption, acute generalized exanthematous pustulosis, Stevens-Johnson syndrome, toxic epidermal necrolysis, subacute cutaneous lupus, and other photosensitivity reactions.[5-7] Of the photosensitivity reactions, both photoallergic and phototoxic reactions to diltiazem have been reported. Phototoxic reactions, as with all drug-induced photosensitivity, have been found to be more common. Scherschun et al[8] in 2001 described 4 cases of photodistributed hyperpigmentation caused by diltiazem. These black women (Fitzpatrick skin types IV–V) presented with reticulated, slate gray, hyperpigmented patches in photodistributed areas. Histopathologic analysis was consistent with interface change, lichenoid dermatitis, and pigment incontinence, similar to our patient's biopsy. All patients had been on diltiazem for an average of 8 months. This review purported UVA as the main culprit, as phototesting of 1 patient yielded a decreased minimal erythema dose to UVA and 2 patients reported darkening of the area when exposed to light through a window, which allows UVA to pass and filters UVB.[8] Since 2001, 8 more cases of diltiazem-induced hyperpigmentation have been reported, not only in black females but also in black males and Hispanics.[9-12] Seven of these 8 cases showed punch biopsies consistent with the findings of our patient, with interface change with vacuolar degeneration, necrotic keratinocytes, and melanophages being amongst the most common findings.[9-12] In 2007, Ramírez et al[13] reported a photoallergic eruption to diltiazem, supported by a positive patch test result.

Drugs that cause photosensitive reactions should exhibit an absorption wavelength in one of the following ranges: UVB (290–320 nm), UVA (320–400 nm),or visible light (>400 nm). As a drug is exposed to one of these light sources, a phototoxic skin response occurs, either through the development of free radicals or through energy transfer causing molecular change.[14] Numerous drugs have been found to cause a photosensitivity hyperpigmentation reaction including amiodarone, tetracyclines, phenothiazines, and imipramine. Studies have shown these drugs to cause phototoxic eruptions upon exposure to the UVA spectrum.[15-17] Throughout the literature, the UVA range

has been reported as the major contributor for photosensitive reactions.[18] Prior studies have shown that diltiazem as a parent compound does not have clinically significant absorption in the UVA, UVB, or visible light ranges, which led authors to hypothesize that an active metabolite of diltiazem was the photosensitizing agent, not the parent compound itself. Saladi et al[12] performed photospectrometry analysis of diltiazem, supporting an effect within the UVB range.

Our case of photodistributed hyperpigmentation to diltiazem is associated with a phototest that showed no reaction to UVA and a slightly reduced minimal erythema dose to UVB. This finding may shed light on the pathogenesis of diltiazem-induced photodistributed hyperpigmentation, with UVB sensitivity possibly playing a role. However, the clinical relevance of this finding has yet to be fully elucidated.

Prior reports have shown diltiazem-induced photosensitivity to be reversible after discontinuation of the drug, which has been proven to be the most effective treatment option.[8-13] For medical management, switching to another calcium channel blocker has been found to be safe, as other calcium channel blockers have not been shown to cause the same photosensitive hyperpigmentation.[6] However, nifedipine has been shown to cause a photosensitivity reaction of unknown mechanism consisting of generalized or localized erythema or maculopapular rash on the face and trunk.[19] Caution is advised when choosing another medication from the same class. For all patients on diltiazem, it is imperative to recommend a broad-spectrum sunscreen, as UVA and UVB radiation may both play a role in diltiazem-induced photodistributed hyperpigmentation.

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