Diltiazem-Associated Photodistributed Hyperpigmentation

A Review of 4 Cases

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Background: Diltiazem hydrochloride is a widely used calcium channel blocking agent. While a few cases of diltiazem-associated photosensitivity have been reported, no cases of photodistributed hyperpigmentation are known.

Observation: Four cases of photodistributed hyperpigmentation associated with the long-acting formulation of diltiazem hydrochloride (Cardizem CD) are presented. All patients were African American women, with a mean age of 62 years. The mean duration of diltiazem administration prior to the development of hyperpigmentation was 8 months. The hyperpigmentation was slate-gray and reticulated. Phototesting during diltiazem therapy revealed a decreased minimal erythema dose to UV-A in 1 patient. Histopathologic examination showed lichenoid dermatitis with prominent pigmentary incontinence. Electron microscopic examination of the tissue revealed multiple melanosome complexes. Discontinuation of diltiazem therapy resulted in the gradual resolution of the hyperpigmentation.

Conclusions: Long-term administration of diltiazem may be associated with characteristic reticulated, slate-gray hyperpigmentation on sun-exposed areas. Discontinuation of the therapy results in resolution of the eruption.

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Diltiazem hydrochloride is a benzothiazepine calcium channel blocking agent that is widely used in the treatment of angina and hypertension. Cutaneous adverse effects associated with the use of diltiazem are rare, but varied. Most commonly reported eruptions include urticaria, pruritus, and maculopapular eruption.1 However, more serious reactions, such as Stevens-Johnson syndrome,2 toxic epidermal necrolysis,3 and vasculitis,4 have also been documented. Only a few cases of diltiazem-associated photosensitivity have been reported5-7; no cases of photodistributed hyperpigmentation are known. Herein, we summarize the clinical course of 4 patients who presented to the dermatology clinic at Henry Ford Hospital, Detroit, Mich, over a 2-year period (April 1998–November 1999) with an unusual photodistributed reticulated hyperpigmentation that developed while they were taking the long-acting formulation of diltiazem hydrochloride (Cardizem CD). All 4 patients were African American women, with a mean age of 62 years (age range, 49-72 years) (Table 1). The mean duration of diltiazem administration prior to the development of hyperpigmentation was 8 months, with a range of 6 to 11 months. The clinical course and evaluation of all patients are summarized in Table 2. All patients showed photodistributed, reticulated, blue-gray pigmentation (Figure 1 and Figure 2). Two of the cases are outlined below.

REPORT OF CASES

CASE 1

A 49 year-old African American woman (Fitzpatrick skin phototype V) presented with a 5-year history of asymptomatic, progressive darkening of the face and neck. According to her medical history, the hyperpigmentation started approximately 6 months after she began diltiazem hydrochloride therapy (120 mg/d).

Physical examination showed reticulated, slate-gray hyperpigmented patches on the labella, malar eminences, anterior aspect of the neck, “V” area of the upper part of the chest, distal aspect of the arms, and hands. There was notable sparing of the nasolabial folds, submental regions, and posterior auricular triangles bilaterally.
Table 1. Demographic and Clinical Data of Patients With Diltiazem-Associated Hyperpigmentation

<table>
<thead>
<tr>
<th>Case No./Sex/Age, y</th>
<th>Fitzpatrick Skin Phototype</th>
<th>Onset After Initiation of Diltiazem Hydrochloride Therapy, mo</th>
<th>Distribution</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/F/49</td>
<td>V</td>
<td>6</td>
<td>Face, neck, chest, forearms, hands</td>
</tr>
<tr>
<td>2/F/72</td>
<td>IV</td>
<td>11</td>
<td>Face, neck, chest</td>
</tr>
<tr>
<td>3/F/56</td>
<td>V</td>
<td>8</td>
<td>Face, neck</td>
</tr>
<tr>
<td>4/F/71</td>
<td>V</td>
<td>7</td>
<td>Face, neck, forearms</td>
</tr>
</tbody>
</table>

Table 2. Evaluation, Management, and Clinical Course of 4 Cases of Diltiazem-Associated Hyperpigmentation*

<table>
<thead>
<tr>
<th>Case No.</th>
<th>UV-B</th>
<th>UV-A</th>
<th>Visible</th>
<th>Follow-Up</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Normal</td>
<td>Decreased†</td>
<td>Normal</td>
<td>80% Improvement at 12 mo</td>
</tr>
<tr>
<td>2</td>
<td>Normal‡</td>
<td>Normal†</td>
<td>Normal‡</td>
<td>30% Improvement at 5 mo</td>
</tr>
<tr>
<td>3</td>
<td>Normal‡</td>
<td>Normal†</td>
<td>Normal‡</td>
<td>50% Improvement at 10 mo</td>
</tr>
<tr>
<td>4</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Newly diagnosed</td>
</tr>
</tbody>
</table>

*Topical therapy in all cases consisted of 4% hydroquinone.
†Minimal erythema dose to UV-A was 18 J/cm² (normal for Fitzpatrick skin phototype V, >40 J/cm²).
‡Performed several days after the discontinuation of diltiazem hydrochloride therapy.

The results of the following laboratory investigations were normal or negative: complete blood cell count, liver function tests, determination of serum urea nitrogen and creatinine levels, and serologic tests for antinuclear antibodies. Phototesting, using a previously described method, was performed while the patient was still taking diltiazem and showed that the minimal erythema dose (MED) to UV-B and the response to visible light were normal. A reduced MED to UV-A was noted at 24 hours (confluent erythema at 18 J/cm²; normal for Fitzpatrick skin phototype V, >40 J/cm²). Photodistributed hyperpigmentation due to diltiazem use was suspected. The patient’s internist told her to discontinue the diltiazem therapy and to begin losartan potassium therapy. Photoprotection and 4% hydroquinone cream were also prescribed.

CASE 2

A 72-year-old African American woman (Fitzpatrick skin phototype IV) presented with an 8-year history of asymptomatic facial hyperpigmentation that had begun 11 months after she had started taking diltiazem hydrochloride (300 mg/d). She noted sustained darkening of the pigmented patches after she had started taking diltiazem (300 mg/d). She noted sustained darkening of the pigmented patches when she was exposed to window-glass–filtered light. Concomitant medications included daily aspirin and ibuprofen. She denied the consistent use of any cosmetics or fragrances.

The patient had blue-gray, reticulated hyperpigmented patches on her face, neck, and chest and on the distal aspect of her arms. A sharply demarcated patch involved the entire “V” of the upper chest area. There was sparing of the skin folds, posterior auricular triangles, upper part of the ears, and submental region (Figure 2).

Laboratory testing revealed that the patient’s liver function test results, complete blood cell count, and serum urea nitrogen and creatinine levels were normal. Phototesting was performed 2 weeks after discontinuation of diltiazem therapy and showed that the MED to UV-A and UV-B and the response to visible light were normal.

Management of the hyperpigmentation consisted of the replacement of diltiazem with clonidine hydrochloride, photoprotection, and twice-daily applications of a 4% hydroquinone cream.

RESULTS

Biopsy specimens from involved areas in cases 1 and 2 showed similar changes. There was an expansion of the papillary dermis by a loosely textured connective tissue stroma with prominent and dilated thin-walled vasculature (Figure 3 and Figure 4). There were focal interstitial and superficial perivascular infiltrates of inflammatory cells, predominantly composed of lymphocytes. In the papillary dermis, there were many scattered pigment-laden cells with occasional thin dendritic processes. The overlying epidermis was thin, with effaced rete ridges. There were focal interface vascular changes with small groups of hyaline globules in the uppermost papillary dermis. These changes are consistent with lichenoid dermatitis with basal vacuolar alteration and prominent pigmentary incontinence.

A thioflavin T stain was negative for amyloid in the hyaline globules in the dermis. Dermal pigment-laden cells stained positively with Fontana-Masson stain and negatively with Prussian blue stain, suggesting that the pigments were melanin but not iron. The finding that the pigments were melanin was further supported by the fact that pigments were completely bleached with 0.3% potassium permanganate for 20 minutes. Immunohistochemical studies performed on bleached sections showed negative staining for S100 antigen (present on dermal melanocytes and Langerhans cells).

Electron microscopic examination revealed a well-preserved cellular architecture. Pigmented cells in the dermis were oval or elongated, with abundant cytoplasm and occasional slender cytoplasmic projections. In the cytoplasm, there were numerous membrane-bound granular matrices containing elliptical, electron-dense granules, representative of melanosome complexes. No internal structures were found in these fully melanized melanosomes (Figure 5). No drug or metabolite deposits were noted. These findings were consistent with a resolving stage of lichenoid dermatitis with prominent pigmentary incontinence.

COMMENT

Diltiazem is a widely used antihypertensive agent. Eruptions after sun exposure associated with diltiazem use have been reported in 3 cases. Hashimoto et al described the development of a pruritic lichenoid eruption in a 70-year-old Japanese farmer. The patient reported aggrav-
tion of his eruption after sun exposure. His symptoms and eruption were reproduced by exogenous UV-A exposure with concurrent diltiazem oral rechallenge. Young et al reported a case of severe generalized erythema with concomitant psoralen–UV-A photochemotherapy that was temporally related to diltiazem administration. The patient, a 76-year-old woman, had received psoralen–UV-A for psoriasis 1 year earlier, without any complications; however, before she began her second course of psoralen–UV-A she began taking diltiazem for hypertension and developed severe erythema shortly thereafter. After discontinuing diltiazem therapy, she restarted treatment with psoralen–UV-A, without incident. Seggev and Lagstein described a 32-year-old man who began taking diltiazem after having a myocardial infarction. The patient developed a photodistributed, papular, dusky-red eruption 1 week after taking the first dose of diltiazem. His eruption completely cleared after he stopped taking diltiazem. To our knowledge, there are no published reports of diltiazem-associated hyperpigmentation in sun-exposed areas.

The history and clinical presentation of our patients implicate UV-A as a causal agent. Two of our patients reported appreciable sustained darkening of their hyperpigmented patches when they were exposed to window-glass–filtered light. Window glass filters UV-B light and permits UV-A light to penetrate. Furthermore, a reduced MED to UV-A was observed in 1 of our 4 pa-

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**Figure 1.** A 72-year-old African American woman (case 2) with slate-gray, grossly reticulated, hyperpigmented patches on her face and neck. Note the sparing of the upper ear area and the posterior auricular triangle.

**Figure 2.** A 56-year-old African American woman (case 3) with dark slate-blue confluent hyperpigmentation on her face. Note the reticular pattern at the periphery of the lesion.

**Figure 3.** There is an expansion of the papillary dermis, with sparse inflammatory cells, as well as superficial perivascular and periadnexal lymphocytic infiltrates. The arrows indicate foci of vacuolar change at the dermoepidermal interface (hematoxylin-eosin, original magnification ×40).

**Figure 4.** Interface vacuolar change (arrow) and dermal pigment-laden cells (arrowhead) admixed with sparse inflammatory cells (hematoxylin-eosin, original magnification ×400).
patients. The fact that 2 of the patients had normal phototesting results may be explained by a delay in the phototesting, which was performed several days after the discontinuation of diltiazem therapy. Based on spectrophotometric data, previous authors have hypothesized that a metabolite may be the actual photosensitizer. The in vitro absorption spectrum of diltiazem is under 300 nm; therefore, the diltiazem parent compound does not have significant absorption in the UV-B (290-320 nm), UV-A (320-400 nm), and visible light (>400 nm) ranges. The putative metabolite responsible for photosensitivity has not been identified; no information is known about its elimination half-life. The half-life of the diltiazem parent compound is 20 hours; hence, the majority of the parent compound would be eliminated in approximately 4 half-lives, which is less than 4 days. The rapid elimination of diltiazem may explain the normalization of the phototest results in these patients.

Although many questions remain unanswered, some conclusions can be reached from these 4 cases. In each case, there was a long interval between the initiation of diltiazem therapy and the emergence of the hyperpigmentation. Normalization of pigmentation does occur, albeit slowly. All 4 patients were African American women. Approximately 80% of our clinic population is African American; therefore, it is unclear whether this observation is of clinical significance, or is attributable to sampling bias. In all 4 patients, the morphological appearance of the hyperpigmentation is most distinctive: slate-gray to blue-gray and reticulated. These features are noticeably different than those of other drug- or chemical-induced photosensitized hyperpigmentation. Amiodarone, chlorpromazine, imipramine, and desipramine induce slate-gray macules or patches. Minocycline hydrochloride induces hyperpigmentation in areas of cutaneous inflammation, typically in acne scars. Argyrria induces slate-gray pigmentation in sun-exposed areas, lunulae of nails, mucous membranes, and sclerae. Histopathologic and electron microscopic examinations of many of these processes show deposits of drugs or metabolites, which were not observed in our patients. Riehl melanosis, or female facial melanosis, also presents with reticular hyperpigmentation of the face. On histopathologic examination, there is increased melanin. However, this condition is caused by contact dermatitis or photocontact dermatitis related to cosmetic products, usually fragrances.

Replacement of diltiazem with another antihypertensive agent is an important step in the treatment of patients who develop hyperpigmentation. Because a cross-reactivity exists among various calcium channel blocking agents, this class of drugs should probably best be avoided altogether when substituting medications. Also, photo-protective measures should be initiated, including the use of a UV-B– and UV-A–absorbing or blocking sunscreen. A hydroquinone cream or other bleaching agent may be prescribed to minimize epidermal melanin formation, since melanin is the deposited pigment. Finally, the patient should be reassured that with proper management, the hyperpigmentation is a reversible process.

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REFERENCES