Diltiazem Induces Severe Photodistributed Hyperpigmentation

Case Series, Histoimmunopathology, Management, and Review of the Literature

Rao N. Saladi, MD; Steven R. Cohen, MD; Robert G. Phelps, MD; Andrea N. Persaud, MD; Donald Rudikoff, MD

Background: Diltiazem hydrochloride is a commonly prescribed benzothiazepine calcium channel blocker for the treatment of cardiovascular disease. Recently, 8 cases of diltiazem-induced photodistributed hyperpigmentation occurring predominantly in elderly African American women were reported. Here, we report occurrence for the first time in a light-skinned African American woman and a Hispanic woman. We also report this finding in an African American man. Biopsy specimens of hyperpigmented areas were obtained for histopathologic evaluation and marker studies. Photospectrometry analysis for diltiazem was performed to analyze the photoabsorption properties of this drug.

Observations: Routine laboratory examination results were normal in all patients. Serologic test results for antinuclear antibodies, including Sjögren antibodies anti-Ro (SS-A) and anti-La (SS-B), were negative. Histopathologic analysis of the skin biopsy specimens revealed a sparse lichenoid infiltrate, prominent pigmentation incontinence, and numerous melanophages in the dermis. There was no increase in dermal mucin suggestive of lupus. The mononuclear cells in the specimens were strongly positive for CD3, weakly positive for CD68, and either weakly positive or negative for CD79a. All specimens were negative for Alcian blue staining. Photospectrometry analysis of diltiazem showed an absorption range within the UV-B spectrum.

Conclusions: Photospectrometry analysis revealed diltiazem could demonstrate a photosensitizing effect within the UV-B range. Discontinuation of therapy with diltiazem is the most effective modality in resolving hyperpigmentation. Avoidance of sun exposure and consistent use of sunscreens and sun-protective clothing are indicated for patients undergoing diltiazem therapy.

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The US Food and Drug Administration approved 3 new calcium channel blockers (nifedipine, verapamil hydrochloride, and diltiazem hydrochloride) in the 1970s and 1980s for treating cardiovascular diseases. Diltiazem, a benzothiazepine, is a widely prescribed agent used in treating hypertension and angina. Adverse effects of the drug include rare cutaneous eruptions such as maculopapular rashes, urticaria, and pruritus. Even rarer severe adverse effects include subacute cutaneous lupus erythematosus, Stevens-Johnson syndrome, toxic epidermal necrolysis, and vasculitis. Photosensitivity reactions of the skin associated with diltiazem rarely have been reported. Diltiazem-induced photodistributed hyperpigmentation has been reported, until now, in 8 cases occurring mostly in African American women. We report occurrence for the first time in a light-skinned African American woman and a Hispanic woman. We also report this finding in an African American man.

REPORT OF CASES

All 4 patients were seen at dermatology clinics affiliated with the Mount Sinai School of Medicine in New York, with a chief complaint of increased pigmentation on the face. The demographic characteristics of the individual patients are described in Table 1. Duration of pigmentation ranged from 6 to 24 months. There were no associated local or systemic symptoms. The patients' medical histories were remarkable for hypertension treated with diltiazem but no use of other medications that could be implicated as a cause for hyperpigmentation. Physical examination in all patients revealed diffuse slate-gray to gray-blue pigmented macules and patches on the face, neck, and forearms (Figure 1). Perifollicular accentuation was noted.

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clinically in several patients (Figure 1). A sharply demarcated hyperpigmented patch demonstrating a V shape was noted in 3 of 4 patients on the upper chest or neck (Figure 1). No periorbital edema or erythema and no periungual erythema or telangiectasia were present. After query, patients revealed a mild to moderate history of exposure to sunlight during diltiazem therapy.

Results of routine laboratory testing in all patients, including a complete blood cell count, liver function tests, serum urea nitrogen and creatinine levels, complete metabolic profile, and thyroid function tests, were all normal. Serologic test results for antinuclear antibodies, including Sjögren antibodies anti-Ro (SS-A) and anti-La (SS-B), were negative.

Skin biopsy specimens of the hyperpigmented areas were obtained, and histopathologic evaluation and marker studies were conducted. Histopathologic findings were similar in all patients. Specimens showed a thinned epi-

<table>
<thead>
<tr>
<th>Source</th>
<th>Case No./Sex/Age, y/Race</th>
<th>Fitzpatrick Skin Phototype</th>
<th>Onset After Initiation of Diltiazem Hydrochloride Therapy, mo</th>
<th>Distribution</th>
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<tbody>
<tr>
<td>Saladi et al</td>
<td>1/F/67/B VI/15</td>
<td>Face, neck, forearms</td>
<td></td>
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<td>2/M/67/B VI/10</td>
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<td>Saladi et al</td>
<td>3/F/50/H III/6</td>
<td>Face, neck, forearms</td>
<td></td>
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<tr>
<td>Saladi et al</td>
<td>4/F/82/W 77/I/1½</td>
<td>Face</td>
<td></td>
<td></td>
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<tr>
<td>Scherschun et al, 2001</td>
<td>5/F/49/B V/6</td>
<td>Face, neck, chest, forearms, hands</td>
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<td>Scherschun et al, 2001</td>
<td>6/F/72/B IV/11</td>
<td>Face, neck, chest</td>
<td></td>
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<td>Scherschun et al, 2001</td>
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<td>Face</td>
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<td>Scherschun et al, 2001</td>
<td>8/F/71/B V/7</td>
<td>Face, neck, forearms</td>
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<td>Chawla and Goyal, 2002</td>
<td>9/F/57/B V/24</td>
<td>Face, neck, back, shins</td>
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<td>Boyer et al, 2003</td>
<td>10/M/71/B VI/12</td>
<td>Face</td>
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<td></td>
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<tr>
<td>Kuykendall-Ivy et al, 2004</td>
<td>11/M/49/H IV/24</td>
<td>Face, neck</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Table 1. Demographic Characteristics of Cases of Photodistributed Hyperpigmentation After Diltiazem Therapy**

*Cases 1 through 4 are the authors’ cases, and cases 5 through 12 are previously reported cases.

**Figure 1.** Distinctive appearance of photodistributed hyperpigmentation in patients undergoing diltiazem hydrochloride therapy (A-I). Hyperpigmentation is consistent with the sun-exposed areas of the face, neck, and forearms. The pigmentation ranges from slate-gray to gray-blue and dark brown. Perifollicular accentuation was noted in some patients.
dermis with effaced rete ridges and focal interface vacuolar changes with small groups of hyaline globules in the uppermost papillary dermis. There were sparse lichenoid changes with interstitial and superficial perivascular infiltrates of inflammatory cells, predominantly composed of lymphocytes. Prominent pigmentary incontinence and numerous melanophages were seen in the dermis (Figure 2A and B). Some biopsy specimens showed perifollicular accentuation, colloid bodies, and association with apoptotic keratinocytes and hydropic changes of the follicular epidermis (Figure 2C). However, none of the biopsy specimens showed increased dermal mucin that might suggest lupus; they were negative for Alcian blue staining. The infiltrating mononuclear cells were strongly CD3 positive (Figure 2D), weakly CD68 positive, and weakly positive or negative for CD79a cells. The CD3-positive cells also showed striking perifollicular extension (Figure 2D).

Photosensitivity reactions associated with the use of diltiazem were reported previously. These cutaneous adverse effects include erythema, pruritus, and/or lichenoid eruptions, which mostly develop soon after exposure to the sun. However, photodistributed hyperpigmentation associated with the use of diltiazem has recently been reported (Table 1). Analysis of all these reported cases in the literature showed that onset of pigmentation changes developed within 6 to 24 months after use of diltiazem. Patient age ranged between 49 and 77 years. Distribution of hyperpigmentation was consistent with sun-exposed areas of the face, neck, and forearms, with lesser pigmentation on the lower chest, back, and shins. Pigmentation was mild to severe with a slate-gray, gray-blue, or dark brown appearance.

To determine the photoabsorption spectrum of diltiazem, photospectrometry analysis of the drug was performed. The results showed diltiazem's absorption range to be 220 to 300 nm, within the UV-B spectrum (Figure 3). These results correlate with previous data showing no absorption in the UV-A spectrum. Although the UV-A range is thought to be the major contributory factor for photosensitivity reactions, several drugs (eg, tetracyclines, thiazides) exert photosensitivity properties in the UV-B range (5%-10% UV-B coexists in sunlight). Furthermore, the pattern of photodistributed pigmentation and history of mild to moderate sun exposure during diltiazem therapy in the patients in our study also supports diltiazem’s photosensitizing effect. In efforts to elicit the causal mechanism, Scherschun et al demonstrated that persistent darkening of hyperpigmented patches occurred in patients exposed only to UV-A. However, electron microscopic evaluation did not reveal drug or metabolite deposits in the skin biopsy specimens; therefore, the authors thought diltiazem may exert its photosensitizing properties through other mechanisms. Several diltiazem metabo-
metabolites have been identified; however, the specific metabolites involved in the adverse effects of the skin are not yet known.16

Generally, for a drug to be regarded as a photosensitizer, the absorption wavelength of the drug should be within the range of UV-B (290-320 nm), UV-A (320-400 nm), and/or visible light (>400 nm).13,15 Drugs that induce photosensitivity hyperpigmentation are activated metabolically (via solar radiation) forming free radicals and reactive intermediates that covalently bind to cellular proteins and DNA. This binding is considered critical in eliciting drug immunotoxicity by producing various enzymatic reactions that trigger a cascade of events, including a release of erythrogenic and pigmentary mediators that result in phototoxic and hyperpigmentary drug reactions.13 Drugs that induce photosensitivity hyperpigmentation include antimicrobial agents (tetracyclines), diuretic agents, psychotropic drugs, antimalarial agents, nonsteroidal anti-inflammatory drugs, cardiovascular drugs, cytotoxic drugs, and other agents.13,17,18 Diltiazem-induced photodistributed hyperpigmentation may be similar to other drug-induced photodistributed hyperpigmentation. Amiodarone, chlorpromazine hydrochloride, imipramine hydrochloride, and desipramine hydrochloride also induce slate-gray macules or patches.19-21 However, diltiazem-induced photodistributed hyperpigmentation can be distinguished from minocycline hydrochloride–induced hyperpigmentation and argyria.22 Minocycline hyperpigmentation appears in areas of cutaneous inflammation, typically in acne scars.22 Argyria induces slate-gray pigmentation not only in sun-exposed areas but also in the lunulae of nails, mucous membranes, and sclerae.23 Patients undergoing treatment with calcium channel blockers such as diltiazem have developed drug-induced subacute cutaneous lupus erythematosus. These patients had positive serologic test results and characteristic subacute cutaneous lupus erythematosus histopathologic findings.24,25

Prevention of diltiazem-induced photodistributed hyperpigmentation can be achieved by initiating photoprotective measures, including use of broad-spectrum sunscreens containing UV-A and UV-B blockers with a sun protection factor of 15 or greater and behavioral modification by limiting sun exposure and wearing sun-protective clothing. Sunscreen use should be initiated at the beginning of diltiazem therapy. If hyperpigmentation develops during diltiazem therapy, discontinuation of diltiazem is the most effective remedy. Better resolution of hyperpigmentation gradually has been observed in patients discontinuing diltiazem10,12 than in those using topical bleaching agents or chemical peels while continuing therapy.11 Application of topical bleaching agents (hydroquinone cream) may be useful in reducing the hyperpigmentation across time. In the patients in our study, use of 4% hydroquinone cream caused partial resolution across time. The patient showed complete clearance of hyperpigmentation after 1 year of diltiazem discontinuation and use of hydroquinone cream. Furthermore, substitution with another calcium channel blocker such as nilodipine14-16 or verapamil17 in patients with adverse cutaneous reactions to diltiazem causes no further complications.

Some conclusions can be drawn on the basis of the cases reported (Table 1 and Table 2). Diltiazem-induced photodistributed hyperpigmentation has been found in other ethnic groups and skin types, but dark-skinned individuals and women were more prone to hyperpigmentation. The association of drug-induced hyperpigmentation in darker skin has never been understood. Results of previous reports and our case series indicate that only patients with severe hyperpigmentation seek dermatological care. Family practitioners, internists, cardiologists, and dermatologists who care for patients using diltiazem should be aware of diltiazem-induced hyperpigmentation and its association with sun exposure. We recommend that these patients limit their sun exposure, wear sun-protective clothing, and use broad-spectrum sunscreen from the start of diltiazem therapy.

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REFERENCES


Table 2. Analytical Observations and Management of Diltiazem-Induced Photodistributed Hyperpigmentation

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Specific Data</th>
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<tr>
<td>Total No. of cases reported</td>
<td>12</td>
</tr>
<tr>
<td>Ethnicity, ratio</td>
<td>African American/all other ethnic groups (~4:1)</td>
</tr>
<tr>
<td>F/M, ratio</td>
<td>3:1</td>
</tr>
<tr>
<td>Mean age, y</td>
<td>63 (range, 49-77)</td>
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<tr>
<td>Site of distribution</td>
<td>Predominantly on sun-exposed (photodistributed) areas: face, neck, and forearms</td>
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<tr>
<td>Mean time of appearance</td>
<td>~12 mo after diltiazem hydrochloride therapy</td>
</tr>
<tr>
<td>Color/appearance</td>
<td>Slate-gray, gray-blue, dark brown, reticulated, macules, patches</td>
</tr>
</tbody>
</table>

Prevention

Sun exposure

Limit during diltiazem hydrochloride therapy

Photoprotective measures

Use broad-spectrum UV-A/UV-B sunscreen and adequate covering of sun-exposed areas from the start of diltiazem hydrochloride therapy

Treatment

Discontinue treatment with diltiazem hydrochloride and/or use topical bleaching agents or chemical peels

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Correction

Error in Figure. In the Study by Juarez et al titled “Analysis of T-Cell Receptor Gene Rearrangement for Predicting Clinical Outcome in Patients With Cutaneous T-Cell Lymphoma: A Comparison of Southern Blot and Polymerase Chain Reaction Methods,” published in the September issue of the ARCHIVES (2005;141:1107-1113), an error occurred in the Figure on page 1110. In the Figure, 2 line markers in the figure key were reversed. The line markers should have indicated that the poorest survival was in the patients with T3/T4 disease, not the patients with T2 disease. The corrected Figure is reproduced here.

Figure. Cumulative survival by skin stage category.