

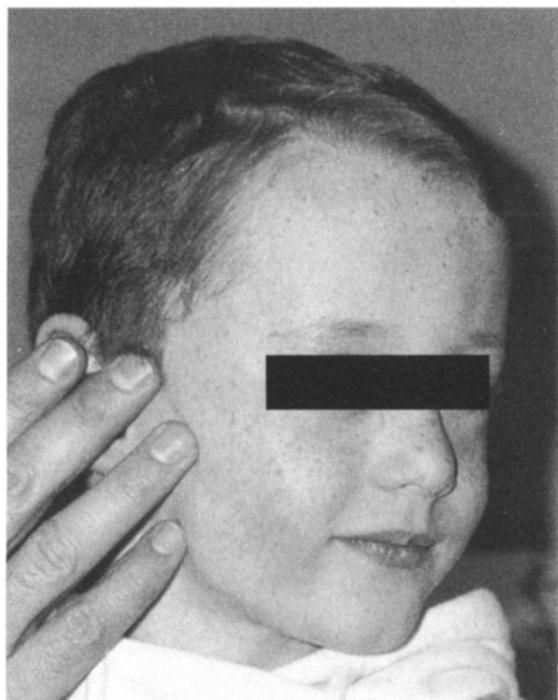


FIG. 1. Open challenge with a tart candy resulted in a band of erythema along the distribution of the right auriculotemporal nerve.

allergy testing. Also, forceps delivery is mentioned in four of the cases and in our case. We are aware of an additional 3-year-old child with this syndrome who was delivered by forceps (personal communication, Robert A. Wood, Baltimore, Md.). In the above-mentioned reports, resolution

of the symptoms was noted in three of four cases at the time of the report.^{3,6} Personal communications with the authors of two of these reports revealed improvement or resolution of symptoms in two of the four cases reported by Beck et al.⁴ and in nine of 10 cases reported by Davis and Strunk³ (including some additional cases). Attempted treatment in adults has included atropine, antihistamines, irradiation, and surgical resection of the auriculotemporal nerve. However, these treatments have been unsuccessful or carry a high risk of complications.¹ Because auriculotemporal syndrome appears to be a benign condition with a good chance of spontaneous remission in children, no specific therapy is recommended. Familiarity with this condition among pediatricians and allergists should help to reduce the misinterpretation of this relatively rare condition as a food allergy.

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Photosensitivity skin reactions to calcium channel blockers

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Reported adverse skin reactions to the administration of calcium channel blockers are rare, up to 8 per 10⁶ prescriptions for nifedipine and diltiazem, consisting mainly of pruritus, rashes, and urticaria.^{1,2} A small number of severe reactions, including vasculitis, exfoliative dermatitis, erythema multiforme, toxic epidermal necrolysis, and Stevens-Johnson syndrome have been described.²⁻⁵ There are only three reports of photosensitivity reactions to nifedipine and one reaction to diltiazem.⁶⁻⁹ We report on a young male patient who

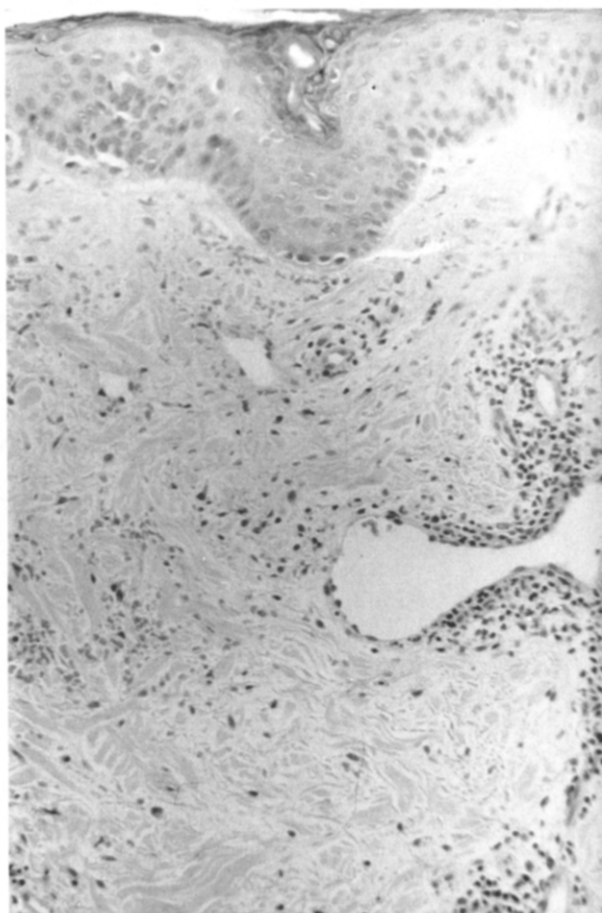


FIG. 1. Biopsy specimen of facial lesion showing a mild reactive surface squamous epithelial change, few intraepithelial lymphocytes, and a prominent granular cell layer. The dermis is edematous with a chronic mononuclear infiltrate, which is mainly perivascular. Extravasated erythrocytes are seen between swollen and disorganized collagen bundles in the lower central portion of the photomicrograph.

had photosensitive reactions to nifedipine and diltiazem.

CASE REPORT

A 32-year-old male security guard and outdoor sports fan had an acute inferior myocardial infarction, which was attributed to coronary artery spasm, because results of coronary angiography were normal. He was started on a regimen of nifedipine, 10 mg four times daily, aspirin, dipyridamole, and nitroglycerin. Two months later, he had another myocardial infarction, and nifedipine was changed to 30 mg of sustained-release (Procardia XL). History was remarkable for allergic rhinitis. After 4 weeks of this treatment (5 months from the start of nifedipine administration), he experienced a nonpruritic, maculopapular rash on the face and anterior neck, fever to 100.6° F, malaise, and dry heaves. The only abnormal laboratory test result was an elevated alanine aminotransferase level. Erythrocyte sedimentation rate and hemolytic complement activity (CH_{50}) were normal,

and antinuclear antibody was not detected. A biopsy specimen of facial skin (Fig. 1) showed sun damage, edema, extravasation of erythrocytes, and a dermal lymphocytic perivascular infiltrate. A photosensitivity reaction was suspected; administration of nifedipine was stopped, and the rash cleared within 3 weeks. Diltiazem (Cardizem CD), 180 mg every day, was substituted. Within 1 week, a papular dusky red rash developed on the face, along with erythema on the neck and anterior chest. Administration of all drugs except diltiazem was stopped because of concern about coronary spasm. Use of loratadine and 2.5% hydrocortisone cream led to minimal improvement. Results of laboratory evaluation including liver and kidney function tests, complete blood count, antinuclear antibody test, erythrocyte sedimentation rate, C_3 , C_4 , CH_{50} , urinary porphyrins and metanephtrins were normal. After 3 weeks of treatment, diltiazem was finally stopped, and complete clearing of skin lesions occurred within 1 week. After another 2 weeks, the patient was challenged with 4 days of dilti-

azem, 180 mg, and only mild facial erythema developed by the fourth day. On the fifth day, a diffuse dusky erythema, with darker colored nodules appeared on the face, neck, and anterior upper chest. Administration of diltiazem was stopped, and use of loratadine and hydrocortisone cream was tried for 3 days, with worsening of the rash, the development of general malaise, and a flare-up of his allergic rhinitis. Erythrocyte sedimentation rate was 18 mm/hr; antinuclear antibody was not detected; and C_3 , C_4 , CH_{50} were normal. All symptoms and lesions reversed within 48 hours of prednisone therapy, 40 mg daily. Prednisone dose was tapered over 1 week. The patient has been receiving maintenance therapy with nitrates, dipyridamole, and aspirin without recurrence of symptoms for 1 year.

DISCUSSION

Our patient's clinical course, the anatomic distribution of the skin lesions, and their recurrence on challenge confirm that photosensitivity to diltiazem was responsible for the adverse reaction. The patient was not challenged with nifedipine, but the similarity of the symptoms and localization of the skin lesions, which disappeared with discontinuation of the drug, strongly suggest a photosensitive reaction to nifedipine as well. Furthermore, the skin biopsy specimen, obtained while the patient was receiving nifedipine, was compatible with a photosensitivity reaction with a mononuclear dermal infiltrate, more prominent around blood vessels with extension into the epidermis. The lesions were restricted to the areas that were continuously exposed to sun because of the patient's work outdoors. A MEDLINE search revealed only three reports of photosensitivity to nifedipine and one reaction to diltiazem.⁶⁻⁹ Two patients treated with nifedipine had photodermatitis on sun-exposed areas, which was confirmed by rechallenge with the drug.⁶ Another two patients had blistering skin rashes on sun-exposed areas after sunbathing but were not challenged.⁷ Another two patients had photodistributed telangiectasia, which improved with discontinuation of nifedipine and recurred with amlodipine.⁸ A single case of photosensitive lichen planus associated with diltiazem was reported.⁹ The reaction could be reproduced with challenge and exposure to UV-A light. Results of photo-patch testing were negative, and the reaction was postulated to be due to a metabolite.⁹ The pathogenetic mechanism for these reactions is unclear. Nifedipine has been shown to be photodegradable in various aerobic conditions *in vitro*, but the concentrations required are higher than those that can be attained *in vivo*.^{10, 11} Still,

the long time required for the occurrence of a reaction to nifedipine (5 months) and the rapid recurrence of a reaction with the administration of diltiazem (within 1 week) suggest a photosensitive and not a phototoxic reaction. The perivascular infiltration with mononuclear cells suggests involvement of the cellular immune system; formation of an antigen by a photoreactive drug or metabolite to bind with skin proteins, leading to a UV-dependent delayed hypersensitivity reaction, could explain the reaction. Still, the exact mechanism is unknown (see below).

Considering the widespread use of calcium channel blockers, the number of reported adverse skin reactions is fairly low. Between 1982 and 1985, 22 cases of urticaria and 17 (out of 25.49×10^6 prescriptions) cases of exfoliative dermatitis, erythema multiform, and Stevens-Johnson syndrome were reported to be caused by nifedipine.¹ The corresponding numbers for diltiazem were 12 and 15, respectively, and one case of toxic epidermal necrolysis was reported (out of 11.12×10^6 prescriptions).¹ Nonspecific rashes were more frequent, but overall adverse skin reactions did not exceed nine per 1,000,000 prescriptions.¹ Isolated cases of fever, generalized lymphadenopathy, and liver toxicity have been reported.² Several cases of widespread skin rashes and cutaneous vasculitis in response to both nifedipine and diltiazem have been reported since the 1989 review.²⁻⁵ Skin biopsy specimens revealed spongiosis, dilated capillaries, and infiltrates consisting of mononuclear cells and eosinophils.³⁻⁵ Results of patch testing with diltiazem were positive in those three reports. Although a delayed-type hypersensitivity reaction is suggested, those patients had no photosensitive reactions.³⁻⁵

Physicians should be aware of these rare but significant photosensitivity skin and systemic reactions to calcium channel blockers. Furthermore, there is a poorly understood cross-reactivity between calcium channel blockers that are structurally unrelated, such as nifedipine and amlodipine,⁸ and now between nifedipine and diltiazem.

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Nizatidine anaphylaxis

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Nizatidine is a powerful specific H_2 receptor antagonist.¹ Like cimetidine, ranitidine, and famotidine, it belongs to the group of imidazole derivatives.

We therefore considered it interesting to report the case of a female patient who complained of a series of clinical signs suggesting anaphylaxis, although subsequent tolerance to other anti- H_2 drugs was good.

CASE REPORT

A 59-year-old woman, with a personal history of diabetes mellitus, gastroduodenal ulcer, and hiatal hernia experienced acute urticaria, odynophagia, laryngeal stridor, dyspnea, angioedema of the lips and tongue, dizziness, and hypotension, 30 to 40 minutes after taking the first dose of nizatidine (Distaxid, 300 mg capsules). She required urgent medical treatment and was subsequently referred to the emergency department of our hospital.

On arrival, she had a blood pressure of 160/80 mm Hg, normal lung auscultation, and clear improvement of laryngeal stridor, although a moderate residual urticaria persisted.

METHODS

The patient and 10 healthy control subjects were included in a double-blind skin prick test, which was done on the upper forearm with cimetidine (4 mg/ml), ranitidine (10 mg/ml), famotidine (10 mg/ml), and nizatidine (10 mg/ml). All skin prick test results were negative. Neither the patient nor any control subject was taking or had taken any medication that could interfere with the results of these tests.

Intradermal skin tests were performed with nizatidine at various concentrations (1:100,000, 1:50,000, 1:10,000, and 1:1000), which were obtained by diluting nizatidine in saline solution (prepared on the day of testing). A positive intradermal reaction was observed in the patient at the concentrations of 1:10,000 and 1:1000. This test result was negative in the control subjects.

After obtaining the patient's written informed consent, we performed oral challenge tests with increasing doses of anti- H_2 drugs, the excipients of the Distaxid 300 mg capsule (starch powder, free-flowing starch, povidone 90, sodium carboxymethylcellulose, free-flowing silicone, and talc) and with the capsule emptied of the preparation, until the therapeutic dose was reached, according to a single-blind method. The doses were

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