

Positive Patch- and Photopatch-Test Reactions to Methylene Bis-Benzotriazolyl Tetramethylbutylphenol in Patients with Both Atopic Dermatitis and Chronic Actinic Dermatitis

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Ultraviolet filters are the most common topical photoallergens. Although currently not available on the US market, methylene bis-benzotriazolyl tetramethylbutylphenol (referred to as bisoctrizole on product labels) represents a new class of UV filters that have both organic and inorganic properties and are widely available in different preparations in Europe, South America, and Asia. We report two patients with atopic dermatitis and chronic actinic dermatitis who had positive patch- and photopatch-test reactions, which suggested both an allergic contact and a photoallergic contact dermatitis from bisoctrizole. Neither patient could identify previous or current contact with the chemical; nonetheless, it is possible that either the allergic contact or photoallergic contact dermatitis from bisoctrizole led to their chronic actinic dermatitis.

IN THE LAST 20 YEARS, there has been a surge in the manufacturing and development of ultraviolet (UV) filters and in the use of sunscreens as the general population is recognizing the photocarcinogenic and photoaging properties of UV radiation. Although many of the newer UV filters are not yet available in the United States, they are easily accessed in other countries and via the virtual worldwide marketplace. Methylene bis-benzotriazolyl tetramethylbutylphenol, which is not available in the United States, is a newer UV filter that functions as both a physical and chemical blocker and is easily blended into various formulations because of its transparency.

The two patients described in this report had longstanding atopic dermatitis and a recent history of persistent photosensitivity. Phototests confirmed chronic actinic dermatitis, and an updated patch and photopatch test panel that included the newer UV filters showed both positive patch- and photopatch-test reactions to methylene bis-benzotriazolyl tetramethylbutylphenol, which suggested both an allergic contact dermatitis and a photoallergic contact dermatitis.

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Case 1

A 52-year-old Caucasian man (skin phototype I) who experienced the onset of atopic dermatitis in childhood presented for the evaluation of a persistent pruritic eruption on his face, neck, and upper extremities that had gradually been worsening for 1 year. He experienced increased symptoms in the spring and summer. Before this, his atopic dermatitis had been well-controlled with the use of mycophenolate mofetil 500 mg three times daily. His medical history included allergic rhinitis, asthma, and hypertension. His medications included valsartan, verapamil, and tramadol, and he had allergies to cat dander, iodine, and penicillin. He also had a history of melanoma and several nonmelanoma skin cancers. The patient worked as a lithographer and reported exposures to solvents and dyes in his daily workplace. Treatment with tacrolimus ointment, topical glucocorticoids, and etanercept resulted in minimal improvement. Despite continued use of mycophenolate mofetil, avid photoprotection with Aubrey Green Tea Moisturizer (Aubrey Organics, Tampa, FL) with sun protection factor (SPF) 15 and CVS Sunscreen with SPF 30 (CVS Corporation, Woonsocket, RI), he continued to have a persistent photoexacerbated eczematous dermatitis.

On cutaneous examination, there were scattered, erythematous, and hyperpigmented papules and thin plaques on the face, neck, and extensor aspects of the upper extremities.

Phototests showed low minimal erythema dose (MED) to ultraviolet A (UVA) light of 15 J/cm², a low MED to narrowband ultraviolet B (nbUVB) of 100 mJ/cm², and a negative reaction to visible light. These phototest reactions were interpreted as chronic actinic dermatitis (CAD). Photopatch tests were performed with the New York University (NYU) Charles C. Harris Skin and Cancer Unit Photoallergen and Sunscreen series (Table 1 and Table 2). Patches were applied in duplicate on the back. After 24 hours, one set of patches was removed and the other was covered with a light impermeable occlusive

Table 1. New York University Charles C. Harris Skin and Cancer Unit Sunscreen Series

<i>Allergen</i>	<i>Concentration and Diluent</i>
4-tert-Butyl-4'-methoxydibenzoylmethane (Parsol 1789)	10% pet
para-Aminobenzoic acid (PABA)	10% pet
Homomenthylsalicylate (homosalate)	5% pet
3-(4-Methylbenzylidene) camphor (Eusolex 6300)	10% pet
2-Ethylhexyl-4-dimethylaminobenzoate (Eusolex 6007)	10% pet
2-Hydroxy-4-methoxybenzophenone (Eusolex 4360)	10% pet
2-Ethylhexyl-4-methoxycinnamate (Parsol MCX)	10% pet
2-Hydroxy-4-methoxy-4-methylbenzophenone (mexenone)	10% pet
Phenylbenzimidazole-5-sulfonic acid (Eusolex 232)	10% pet
2-Hydroxy-4-methoxybenzophenone-5-sulfonic acid (sulisobenzene, BZP-4)	10% pet
Drometrizole trisiloxane	10% pet
Octocrylene	10% pet
Octyl salicylate	5% pet
Octyltriazone	10% pet
Isoamyl-p-methoxycinnamate	10% pet
Bis-ethylhexyloxyphenol methoxyphenyl triazine	10% pet
Methylene bis-benzotriazolyl tetramethylbutylphenol	10% pet
2-(4-Diethylamino-2-hydroxybenzoyl)-benzoic acid	10% pet
Diethylhexyl butamido triazone (Uvasorb HEP)	10% pet
Disodium phenyldibenzimidazole tetrasulfon	10% pet
Petrolatum control	—

pet = petrolatum.

Table 2. New York University Charles C. Harris Skin and Cancer Unit Photoallergen Series

<i>Allergen</i>	<i>Concentration and Diluent</i>
<i>Sunscreens</i>	
Octyl methoxycinnamate	7.5% pet
Sulisobenzene (BZP-4)	10% pet
para-Aminobenzoic acid	5% alcohol
Octyl dimethyl PABA	5% alcohol
3-(4-Methylbenzylidene) camphor (Eusolex 6300)	2% pet
Oxybenzone (BZP-3)	3% pet
Menthyl anthranilate	5% pet
<i>Antimicrobial agents</i>	
Bithionol (thiobis-dichlorophenol)	1% pet
Fenticlor (thiobis-chlorophenol)	1% pet
Dichlorophen	1% pet
Triclosan	2% pet
Hexachlorophene	1% pet
Chlorhexidine diacetate	0.5% aq
Sulfanilamide	1% pet
Trichlorocarbanilide	1% pet
Tribromosalicylanilide	1% pet
<i>Medications</i>	
Promethazine	1% pet
Diphenhydramine hydrochloride	1% pet
Chlorpromazine hydrochloride	0.1% pet
<i>Fragrances</i>	
Sandalwood oil	2% pet
Fragrance mix I	8% pet
Fragrance mix II	14% pet
6-Methylcoumarin	1% pet
<i>Plant and plant derivatives</i>	
<i>Chamomilla romana</i>	1% pet
Diallyl disulfide	1% pet
<i>Arnica montana</i>	0.5% pet
<i>Taraxacum officinale</i>	2.5% pet
<i>Achillea millefolium</i>	1% pet
Propolis	10% pet
<i>Chrysanthemum cinerariaefolium</i>	1% pet
Sesquiterpene lactone mix	0.1% pet
α -Methylene- γ -butyrolactone	0.01% pet
<i>Tanacetum vulgare</i>	1% pet
Alantolactone	0.1% pet
Lichen acid mix	0.3% pet
<i>Pesticides</i>	
Captan	0.1% pet
Ziram	1% pet
<i>Other chemicals</i>	
Thiourea (thiocarbamide)	0.1% pet
Petrolatum control	—

aq = aqueous; PABA = para-aminobenzoic acid; pet = petrolatum.

dressings. The uncovered side was then irradiated with 7.5 J/cm^2 of UVA (50% of the MED-A). Twenty-four hours later (48 hours after initial patch placement), the remaining patches were removed and reactions were scored with the International Contact Dermatitis Research Group scoring system.¹ At the 48-hour reading, a ++ edematous reaction to methylene bis-benzotriazolyl tetramethylbutylphenol on the nonirradiated side was noted, and a + reaction was detected on the irradiated side. The 96-hour reading showed a ++ edematous reaction on the irradiated side and a + reaction on the nonirradiated side, which was interpreted as both allergic contact dermatitis (ACD) and photoallergic contact dermatitis (PACD). The remainder of the patch- and photopatch-test results were negative.

Case 2

A 52-year-old African American man (skin phototype IV) with a history of atopic dermatitis in childhood and ACD (he had had previous positive patch-test reactions to paraphenylenediamine, neomycin, bacitracin, fragrance mix, cocamide diethanolamine, and dimethylaminopropylamine) presented for evaluation of a pruritic burning eruption on the face, neck, and extensor surfaces of the upper extremities that had been worsening for 1 year. The patient experienced a worsening of the eruption in the summer. His past medical history included hypertension and shellfish allergy. Medications included atenolol, amlodipine, hydrochlorothiazide, fexofenadine, and hydroxyzine. The patient worked as an accountant and denied having relevant exposures in his workplace. He had been

treated with tacrolimus ointment, topical glucocorticoids, and etanercept, without resolution. Despite the use of topical glucocorticoids, tacrolimus ointment, and photoprotection, as well as avoidance of the contact allergens listed above, the patient continued to experience exacerbations of an eczematous dermatitis on sun-exposed sites.

On cutaneous examination, there were scattered erythematous hyperpigmented papules and thin plaques on the face, neck, and extensor surfaces of the upper extremities.

Phototests showed a low MED of UVB (MED-B) of 350 mJ/cm^2 (nbUVB was used for testing), a normal MED-A of greater than 45 J/cm^2 , and a negative reaction to visible light. These phototest results were interpreted as representing CAD. Photopatch tests were performed with the NYU Charles C. Harris Skin and Cancer Unit photoallergen and sunscreen series, and the uncovered side was irradiated with 10 J/cm^2 of UVA. At 48 hours, a ++ edematous reaction was noted to methylene bis-benzotriazolyl tetramethylbutylphenol on the irradiated side. The 96-hour reading showed a ++ erythematous edematous reaction on the irradiated side and a + reaction on the nonirradiated side, which was interpreted as both ACD and PACD (Fig 1). The results of the remaining patch and photopatch tests were negative.

Discussion

We report on two male patients who have had atopic dermatitis since childhood and who developed a persistent pruritic photosensitive eczematous eruption that was associated with a reduced MED-A and MED-B in case 1

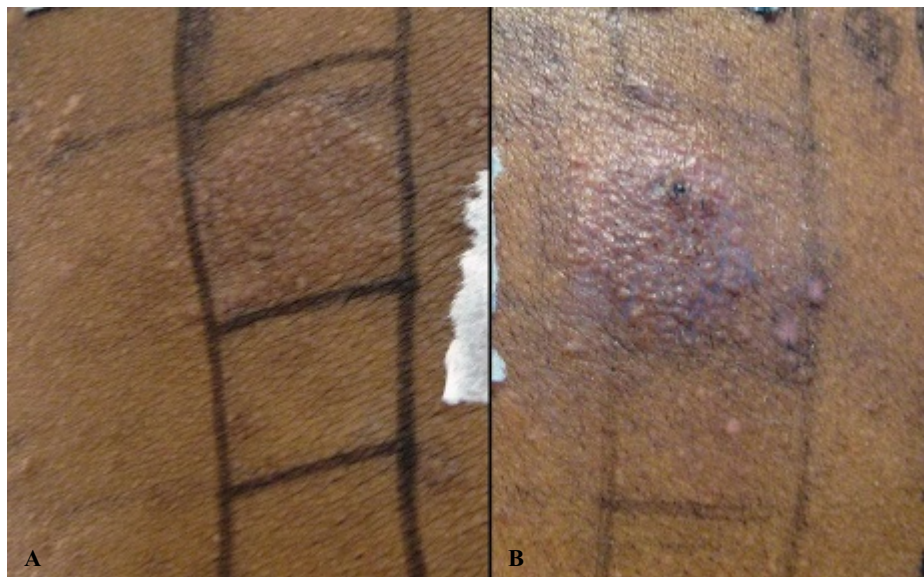


Figure 1. Photopatch-test results for patient 2 at 96 hours after patch placement and 72 hours after irradiation: a + reaction on the nonirradiated side (A) and a ++ erythematous edematous reaction with spreading papules on the ultraviolet-irradiated side (B). These findings are consistent with allergic contact dermatitis and photoallergic contact dermatitis.

and a reduced MED-B in case 2, which was consistent with a diagnosis of CAD. Photopatch tests showed both an ACD and a PACD to methylene bis-benzotriazolyl tetramethylbutylphenol (the International Nomenclature of Cosmetic Ingredients name; “bisotrizole” is used on product labels) in both patients. Although neither patient could identify this ingredient in the products they were currently using, it is possible that both patients had exposure to the chemical in one of the many sunscreens they had previously used.

Owing to repeated use, sunscreens are a frequent cause of PACD in photosensitive patients.² It is plausible that either an ACD or a PACD from bisotrizole (Tinosorb M, Ciba Specialty Chemicals, Lake Peekskill, NY), which may have been present in a sunscreen or another topical product that our patients had previously used, evolved into CAD.

Bisotrizole is an organic compound that provides broad-spectrum UV protection with a maximum UVA and UVB absorption of 360 nm and 305 nm, respectively. Bisotrizole absorbs radiation like an organic compound; it scatters and reflects radiation like an inorganic material. This large (100–200 nm) organic molecule was first developed in Switzerland in 1998 and has been present in different sunscreen and makeup products in Europe since 2000 (Table 3).³ Bisotrizole and a similar chemical, bis-ethylhexyloxyphenol methoxyphenyl triazine (BEMT, Tinosorb S, Ciba Specialty Chemicals), belong to the benzotriazole family of photostable broad-spectrum UV filters, which represents a new class of UV filters that are both organic and insoluble.

To date, there have been two reports of ACD from bisotrizole. In one case, decyl glucoside, a non-ionic

surfactant present in bisotrizole, was found to be the cause of the positive patch-test reaction.⁴ In the second case, decyl glucoside was not tested separately, and positive reactions to bisotrizole were of equal intensity on the photoexposed and nonirradiated sides on days 2 and 4, consistent with ACD.⁵ In both of our cases, a stronger positive reaction was detected on the irradiated side, which indicated both PACD and ACD. Photoaugmentation of a contact allergy rather than the coexistence of ACD and PACD is possible but would be difficult to prove in this case. Over a 10-year period, we have not seen irritant reactions to bisotrizole in our photopatch-tested patients, many of whom had atopic dermatitis. At this time, there are no data on the potential of bisotrizole to cross-react with other chemicals. Further studies on this chemical and the description of more patients with ACD or PACD from bisotrizole will help to further elucidate this possibility.

UV filters in sunscreens remain the most frequently documented topical photoallergens worldwide.⁶ It is not surprising that new sunscreen chemicals have emerged as photoallergens. Benzophenones replaced p-aminobenzoic acid as the most common photoallergen in the 1990s.⁷ More recently, newer UV filters such as octyl-methoxycinnamate,⁸ isoamyl-p-methoxycinnamate,⁹ octyl triazone,¹⁰ 4-tert-butyl-4'-methoxydibenzoylmethane (Parsol 1789),¹¹ and 2-ethylhexyl-p-methoxycinnamate (Parsol MCX) have been implicated in PACD.

Bisotrizole is present in numerous sunscreens, cosmetics, and skin-lightening formulations that are available in Europe and South America, but it is not currently included in the US Food and Drug Administration (FDA) over-the-counter (OTC) sunscreen monograph¹² (Table 4). A petition for the inclusion of the chemical into the OTC

Table 3. Products Containing Bisotrizole

<i>Brand (Manufacturer)</i>	<i>Product</i>	<i>Where Available</i>
Piz Buin (Johnson & Johnson, New Brunswick, NJ)	Sun Allergy Lotion 30 In Sun Lotion (8+) 15 Mountain Sun Cream 15 & 30	Switzerland
Roc (Johnson & Johnson)	Minesol Sun Lotion 20 Minesol Sun Cream 30 Minesol Sun Block Lotion 40 Minesol Sun Block Cream 60	France
Suncare Gel (Grunenthal Tecnandian SA, Ecuador, Quito, Ecuador)	Suncare-Gel SPF 60	Ecuador
Tanga (Laboratorios Recamier Ltda Peru, Cali, Columbia)	Tanga-Sport SPF 24 Tanga-Kids SPF 50	Colombia
OHUI Sun Science Powder (LG Household and Healthcare, Inc., Seoul, South Korea)	Powder Sunblock EX SPF 50 Sun Block Natural Skin	Asia

Table 4. Ultraviolet Filters Included in the Most Recent U.S. Food and Drug Administration Sunscreen Over-the-Counter Monograph

<i>Ultraviolet Filter</i>	<i>Maximum Concentration (%)</i>
para-Aminobenzoic acid (PABA)	15
Avobenzone	3
Cinoxate	3
Dioxybenzone	3
Ecamsule (terephthalylidene dicamphor sulfonic acid)	10
Homosalate	15
Menthyl anthranilate	5
Octocrylene	10
Octyl methoxycinnamate	7.5
Octyl salicylate	5
Oxybenzone	6
Padimate O	8
Phenylbenzimidazole sulfonic acid	4
Sulisobenzene	10
Titanium dioxide	25
Trolamine salicylate	12
Zinc oxide	25

Adapted from Collaris EJH, Frank J.¹¹

sunscreen monograph was submitted to the US FDA in 2005 by the Swiss manufacturer, Ciba Specialty Chemicals.¹³ In addition to being a physical blocker, bisoctrizole has increased transparency relative to zinc oxide or titanium dioxide, which makes it an easy and attractive chemical for incorporation into a wide variety of topical preparations. In view of the increasing and instantaneous access to the worldwide marketplace, it is important to be aware of new UV filters as potential photoallergens.

CAD is characterized by a persistent eczematous eruption and a reduced MED to UVB, UVA, or both, and/or a reaction to visible light. Initially, there is a seasonal variation with worsening in the spring and summer; however, the eruption becomes perennial with time. The eruption typically begins on the face and then spreads to other sun-exposed sites.¹⁴ Patients with CAD have an increased incidence of both ACD and PACD.^{15,16} CAD may also evolve in individuals with preexisting dermatitis such as atopic dermatitis or ACD.^{17,18}

Among patients with atopic dermatitis (AD), the incidence of CAD has been estimated to be in the range of 3 to 10%.¹⁹ In a retrospective review of 108 patients, 47% had a polymorphous light eruption-type reaction, and 41% had an eczematous reaction after UV exposure. However, only 13 of the 108 patients demonstrated a low MED (a decreased MED-B in 8 patients and a decreased

MED-A in 5 patients).¹⁹ Although CAD occurred in both of our patients with AD, it appears that CAD is not a common feature in patients with AD.

In the two patients described here, PACD and ACD from bisoctrizole, as well as underlying AD, likely contributed to the development of CAD. In the last 20 years, there has been a surge in the manufacture of UV filters and the use of sunscreens in the general population. Consequently, ACD and PACD from sunscreens have been increasing and continue to have a high prevalence among photosensitive patients. The evaluation of a patient with a photosensitive eruption should include phototests, patch tests, and photopatch tests. This report highlights the need for an awareness of new UV filters (such as bisoctrizole) that are easily attainable despite their not being available locally.

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