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THE NATURE OF TRIBROMOSALICYLANILIDE PHOTOALLERGY*

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ABSTRACT

Three patients with photoallergy to 3,4′,5 tribromosalicylanilide (TBS) following the use of a germicidal soap were studied to determine the mechanism of their photoallergy. None of these subjects had undergone previous patch or photopatch testing. Duplicate patches of purified TBS and its photoproducts 4′,5 dibromosalicylanilide (DBS), 4′ monobromosalicylanilide (MBS), and salicylanilide were applied to the skin of the back. One set of patches was irradiated using a source of long ultraviolet whereas all ultraviolet radiation was rigorously excluded from the second set. In one patient the results were consistent with a plain contact allergy to the photoproducts DBS and MBS. In a second patient irradiation of any of the three brominated salicylanilides resulted in a reaction whereas no reactions were observed in the dark. A free radical mechanism may be responsible for the formation of the complete antigen in this patient. In the third patient both mechanisms appeared to coexist. Reactions to commercial-grade TBS did not differ from those obtained with pure TBS.

There are at least two conflicting views as to the mechanism of photoallergy to 3,4′,5 tribromosalicylanilide (TBS) and to 4′,5 dibromosalicylanilide (DBS).

Willis and Kligman [1], have argued that the sole role of light in photoallergic contact dermatitis to TBS and DBS is to convert the photosensitizer into a more potent contact allergen, especially 4′ monobromosalicylanilide (MBS) which can fully reproduce the reaction in the absence of light. Such a mechanism is thought to be responsible for photoallergy to the sulfanilamide derivative 1-butyl-3-sulfanilamide, whose phototransformation product 4 hydroxyl-amino-benzene sulphonate has been shown to give positive plain patch tests in patients with 1-butyl-3-sulfanilamide photoallergy [2,3].

Willis and Kligman used a maximization technique to induce TBS photoallergy in experimental subjects. These subjects then reacted to DBS and MBS, but not to TBS in the dark. They also found that as contact sensitizers the order of potency was MBS > DBS > TBS and that subjects contact sensitized to DBS or MBS developed positive photopatch tests to TBS. They concluded that the role of light was to transform TBS into either DBS or MBS which in turn elicited allergic contact dermatitis [1].

Other authors hold that irradiation produces highly reactive short-lived free radicals or excited triplet states which combine with protein to form a novel complete antigen (a step conceivably prone to therapeutic intervention). Thus Jung has shown in triacetyldiphenolisatin (TDI) photoallergy that the appropriate ultraviolet radiation results in the formation of a reactive triplet state of TDI which will combine to protein, probably to the amino groups of lysine, forming a TDI protein complex [4, 5]. This complex will elicit an allergic reaction on a photosensitized subject, whereas in the dark TDI will neither complex with protein nor elicit an allergic reaction. Previously irradiated TDI will elicit an allergic reaction only if the solvent allows the excited triplet state to be long lived and if the solution is applied to the skin before the triplet state is fully decayed [5]. Other photoallergens such as tetrachlorsalicylanilide [6] and Jadit [7] will combine with proteins when irradiated but not in the dark. Light-induced Jadit–albumin complexes will induce lymphocyte transformation in cells from subjects with Jadit photoallergy [7]. Harber et al [8] argue that DBS and TBS photosensitivity is analogously due to the combination of a halogenated salicylanilide free-radical, formed upon irradiation, with protein forming a new antigen.

The structural formula for salicylanilide and the numbering system for substitutions is shown in the Figure. This usual isomer used as a germicidal in soaps is 3,4′,5 TBS. The proportion of impurities (mainly 4′,5 DBS, 3,5 DBS, and 3′,3,4′,5 tetrabromosalicylanilide) has steadily dropped from 15% in the early 1960s [9] to less than 2% currently. Coxon et al [10] found that on irradiation with a high-pressure mercury arc with a glass filter (UV > 320 nm) and a partially filtered low-pressure mercury arc (predominantly 254 nm), 3,4′,5 TBS was converted to 4′,5 DBS and then to 4′ MBS. Although they claimed that 4′ MBS was unaffected by near UV, this compound has an absorption maximum around 305 nm [11] and thus does absorb UV wavelengths present in sunlight. Furthermore, irradiation in the 290–320 nm waveband will convert 4′ MBS to salicylanilide which is not

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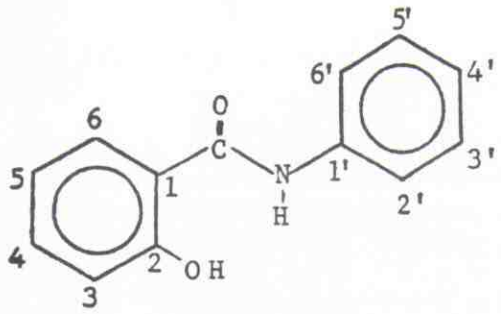

FIGURE: Salicylanilide structure and numbering system.

further degraded by wavelengths present in sunlight.†

Using an iodine-release technique, Coxon et al have shown that the photoconversions from TBS to DBS and DBS to MBS takes place via a free radical mechanism [10]. Although there is no published evidence, it seems likely that MBS photocleavage similarly involves free radical production.

In this study we attempt to resolve the type of mechanism responsible for TBS photoallergy by subjecting patients photosensitized during normal soap usage to photopatch testing and to plain patch testing with chemically pure photoproducts under conditions of rigorous light exclusion. A considerable number of precautions are necessary in a study of this type. The use of chemically pure materials is indicated since there has been prior speculation that TBS itself is not a photosensitizer, the photoallergy being dependent on traces of DBS and tetrabromosalicylanilide present as impurities [12].

A number of authors have commented on the very small amount of UV energy which will provoke photoallergic reactions in highly sensitized individuals [13, 14]. Extreme measures were taken to minimize inadvertent UV exposures on control areas such as might occur through clothing and white adhesive tape [15] or from diffuse room light reaching a subject's back while dressing or undressing [16], leading to the so-called "masked" photopatch test. Patients were studied who had been sensitized to soap in normal usage situations to exclude any possible artefacts in the manner of sensitization introduced by various maximization procedures. Patients were also selected because they had not been subject to previous patch or photopatch testing with halogenated salicylanilides or related materials. It has been shown that either repeated testing [8,9] or the inclusion of tetrachlorosalicylanilide [16] in the testing procedure can increase the number of patch test reactions and possibly induce "masked" photopatch test results.

† Baker FW: Personal communication

MATERIALS AND METHODS

Pure brominated salicylanilides were kindly supplied by the Procter and Gamble Company of Cincinnati, Ohio. The 3,4',5 TBS and 4',5 TBS had been purified by thin-layer chromatography; 4' MBS had been independently synthesized. Salicylanilide was obtained from the Aldrich Chemical Company. The minimal erythema dose (MED) of UV-B was determined using graded exposures from a bank of fluorescent sunlamps (Westinghouse FS40T12). The normal MED for the Caucasian population is from 2.5×10^2 to 5.0×10^2 J/m^2 ($2.5\text{–}5.0 \times 10^4$ μ Wsec/cm^2).

Preparation of each of these compounds at 1% in white petrolatum were made under lighting from Westinghouse 100W Bug-a-way® ultraviolet-free yellow light bulbs. Similar light sources were used for the application and removal of patches, and for the inspection of reactions.

Two sets of patches of each of these materials were applied to the skin of the back using Johnson & Johnson 1½" Band-Aids covered, secured, and occluded by Dermicel® tape. Each area was then covered by silver-coated, polyester-film tape (Scotch® No. 850) to ensure complete occlusion from light. Subjects were instructed not to go in the sun more than absolutely necessary. Twenty-four hours after application, one set of patches was removed, the area cleansed with 70% ethanol solution, and irradiated for 30 min at a distance of 18 inches from a bank of 4 fluorescent black lights (Westinghouse F40BLB). The total radiant exposure at the surface of the skin during this irradiation, measured with an IL 600/620 photometer–photodosimeter (International Light, Inc., Newburyport, Mass.) and detector with a calibrated broad band filter was 1.9×10^4 J/m^2. Immediately after irradiation the area was recovered with silver-coated polyester-film tape. Forty-eight hours after application the control set of patches was removed and cleansed with 70% ethanol. Reactions on irradiated and control areas were evaluated and then both were recovered with the silver-coated polyester-film tape and secured with additional Dermicel® tape. Similar readings of reactions were performed 72 and 120 hr after initial application of the patches.

RESULTS

Pertinent clinical data from the three patients used in this study are given in Table I. In this table, the MED for patient #2, a rather lightly pigmented Negro, was classified as probably normal, as it was within the normal range for Caucasian subjects. Normals for Negroes have not been established.

Each of these subjects used a soap containing TBS and the usage of such a soap seemed closely related either to the onset of or recurrence of the photodermatitis. No other cause for photosensitivity was apparent in any of these patients. It should be noted that the use of antibacterial agents in deodorant soaps varies, and at the time of this writing TBS was no longer an ingredient in Safeguard which now contains 3,4,4' trichlorocarbanilide and 4,4'dichloro-3-(trifluoromethyl) carbanilide, ingredients which on the basis of current information seem less likely to cause photodermatitis.

The reactions observed when these three pa-

TABLE I

Pertinent clinical features of patients

Patient	Race	Age (years)	Sex	Duration of photosensitivity	Soap exposure	Persistence after removal of exposure	MED*	Predominant clinical features
#1	Negro	69	Male	14 months	White Lifebuoy	4 months	Probably normal	Lichenoid dermatitis of exposed areas
#2	Caucasian	33	Male	3 years	Safeguard	6 months	Very low	Erythema or acute eczematous dermatitis of exposed areas
#3	Caucasian	75	Male	12 years	Safeguard	8 months	Low	Lichenoid dermatitis of exposed areas

* Normal MED for Caucasians with UV source used is 2.5×10^2–5.0×10^2 J/m² of radiation < 315 nm.

TABLE II

Reactions to TBS and its photoproducts*

Patient	Irradiation of patches	TBS (commercial†)		TBS (pure)		4′,5 DBS		4′ MBS		Salicylanilide	
		48 hr	120 hr	48 hr	120 hr	48 hr	120 hr	48 hr	120 hr	48 hr	120 hr
#1	Irradiated	3+	3+	3+	3+	3+	3+	3+	4+	0	0
	Dark control	0	0	0	0	0	0	0	0	0	0
#2	Irradiated	3+	3+	3+	3+	4+	3+	4+	3+	0	0
	Dark control	0	0	0	0	3+	0	4+	3+	0	0
#3	Irradiated	3+	3+	2+	3+	2+	3+	4+	4+	0	0
	Dark control	0	0	0	0	0	0	3+	±	0	0

* Reactions were graded according to the following scale: 0 = no reaction, ± = doubtful reaction, 1+ = erythema, 2+ = erythema plus palpable edema or papules, 3+ = erythema plus vesiculation, 4+ = strong vascular reaction spreading beyond patch area.

† Tuasal 100, Dow Chemical Company.

tients were phototested to TBS and TBS photoproducts are recorded in Table II. There were no reactions to irradiation of adjacent areas of skin which were not the sites of patch tests, nor on areas where petrolatum alone was applied. Although the results differ from patient to patient, certain consistent features were seen. The reactions to pure TBS were not appreciably different from the reactions to commercially available TBS, thereby showing that the reactions were not dependent on small quantities of impurities therein. None of the patients reacted to salicylanilide on photopatch or dark-control sites, demonstrating that the final end-product of TBS photodegradation was not an allergen in these subjects.

We observed that patient #1 had no reaction to TBS or any of its photoproducts in the dark. We can conclude that in this patient simple conversion of TBS to a photoproduct which is a contact allergen cannot account for the photoallergy. Excitation by light is clearly necessary to elicit the photoallergy although any one of the three brominated salicylanilides in an excited state could elicit a reaction.

Patient #2 developed more severe reactions to DBS and MBS than to TBS. The reaction to MBS was equally severe whether irradiated or not. Plain contact sensitivity to DBS was also observed which could have been a cross-reaction with MBS contact sensitivity, although the intracutaneous conversion of DBS to MBS in the dark might also be possible. In any case, the reaction to DBS was more severe when this compound was irradiated, possibly because of photoconversion of DBS to MBS. The reactions in this patient were clearly consistent with the hypothesis of Willis and Kligman.

Patient #3 developed reactions which were intermediate between those of the other two patients. Although he reacted to MBS in the dark, the reaction was stronger and persisted much longer after irradiation. It should be noted that this method of phototesting, where a simple contact allergen will be present on a photopatch site for only 24 hr against 48 hr on a control site, will tend to exaggerate results on unirradiated areas. This patient thus appeared to have both contact and photocontact reactivity to MBS. Certainly, MBS

contact allergy alone could not explain these reactions.

DISCUSSION

A number of authors have noted the absence of plain positive patch tests to TBS and DBS on areas adequately shielded from light in patients with photoallergies to these materials [8,17,20]. Only Osmundsen appears to have tested patients sensitized by normal soap usage to the full range of 3,4′,5 TBS photoproducts (4′,5 DBS, 4′ MBS and salicylanilide) [21]. His results were similar to those reported here in that the majority of tested patients reacted to 4′,5 DBS and 4′ MBS when irradiated, but in addition 11 out of 20 patients reacted to 4′ MBS in the dark. He also reported that in a number of patients with positive plain patch tests to 4′ MBS the reactions were intensified by exposure to ultraviolet. A small percentage of patients were sensitive to TBS in the dark, all of whom were also contact sensitive to 4′ MBS [22].

Both the reaction of patient #1 to 4′ MBS only when irradiated, as well as the intensification by ultraviolet exposure of the 4′ MBS reaction in subject #3, are explicable when we consider that irradiated 4′ MBS is thereby converted to salicylanilide, presumably with the formation of highly reactive salicylanilide and bromine radicals. We assume that one of these, probably the salicylanilide radical, combines with an epidermal protein to form a complete antigen in a similar manner to those formed by other irradiated photoallergens.

On the other hand, the presence of plain contact allergy to 4′ MBS in two of these patients demonstrates that such allergy to a TBS photoproduct can occur under conditions of normal soap use and may, as in our patient #2, be adequate to explain the photoallergy.

The reason why Willis and Kligman [1] induced plain contact allergy to 4′ MBS in all those in whom they induced TBS photoallergy may reside in the maximization method used for induction. Irradiation was performed immediately after the application of 10% crystalline TBS to the skin, which had been Scotch® tape stripped prior to the first exposure, though not thereafter. Such a technique must maximize the concentration of photoproducts on the surface of the skin. On the other hand, in the more normal circumstances of soap usage followed sometime later by sun exposure, there would seem to be more opportunity for the halogenated salicylanilide to penetrate the epidermis and consequently for the free-radical species resulting from irradiation to be closely apposed to epidermal protein.

Our results indicate that the impurities present in commercial 3,4′,5 TBS as currently supplied in the United States are unlikely to play a significant role in the elicitation of TBS photoallergy.

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