Poison Ivy/Oak Dermatitis

Use of Polyamine Salts of a Linoleic Acid Dimer for Topical Prophylaxis

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• **Closed patch tests were used to evaluate the ability of 156 different preparations (based on 22 different chemicals) to prevent poison ivy dermatitis. Several polyamine salts of a linoleic acid dimer were identified that were totally able to prevent the usual dermatitis in approximately 70% of subjects. The effectiveness of the preparations improved when the antigen and the protectant were washed off within eight to 12 hours, instead of remaining on the skin for 48 hours. When washed off, and depending on the protectant, concentration, and vehicle used, several of the preparations were totally able to prevent a dermatitis in a range of 56% to 100% of subjects tested. Further work with these compounds may greatly benefit the many people currently plagued by their allergy to poison ivy and poison oak.**

(*Arch Dermatol* 1986;122:783-789)

Poison oak (*Toxicodendron diversilobum*) and poison ivy (*Toxicodendron radicans*) are responsible for a large number of cases of allergic contact dermatitis each year. People at risk include workers in logging, agriculture, forest fire-fighting, construction, and utility maintenance, as well as outdoor enthusiasts. California, in 1979, listed poison oak as the most common causal agent of occupational skin disorders, accounting for approximately 24% of reported cases of occupational skin disease.[1] There are many more cases that go unreported.

The allergenic component of poison ivy, known as *urushiol*, consists primarily of a collection of four similar pentadecylcatechols (Fig 1). These compounds differ only in possessing zero, one, two, or three double bonds.[2] The absolute and relative amount of each compound varies from plant to plant[3] and among different plant parts.[4] The compounds containing two double bonds are present in the greatest concentration and also possess the greatest reactivity, while the completely saturated compound (3-pentadecylcatechol) is the least reactive in humans. Small amounts of the related heptadecylcatechols are also present. Poison oak urushiol is very similar but consists primarily of the heptadecylcatechols, with smaller amounts of the pentadecylcatechols being present.[5] The close chemical similarity of the antigens results in immunologic crossreactivity; thus, individuals who are sensitive to poison oak will be equally sensitive to poison ivy, and vice versa. Studies have shown that the catechol portion of the molecule (the two hydroxyl groups in ortho position) is essential for antigenicity.[6] It is believed that the catechol is oxidized to a more reactive quinone within the skin. The quinone then conjugates body proteins, resulting in the formation of the complete antigen.[7] In vitro work by Liberato et al[8] supports this hypothesis.

There are three possible approaches to the prevention of poison oak and poison ivy dermatitis. The most desirable approach would be to induce tolerance in nonsensitized individuals. This involves preventing sensitization from ever occurring. Epstein et al[9] have shown that this is possible using weekly intramuscular injections of a poison ivy-olive oil preparation.[9] However, three to five years after attempted sensitization, half of their study group had become reactive. Their study population consisted of institutionalized children whose only exposures to poison oak/ivy occurred as part of the testing protocol. Had the children experienced more frequent exposures, as is clinically more common, it is not known whether they would have acted as boosters to maintain tolerance or if they would have hastened the decline in tolerance.

Accepted for publication Feb 5, 1986.

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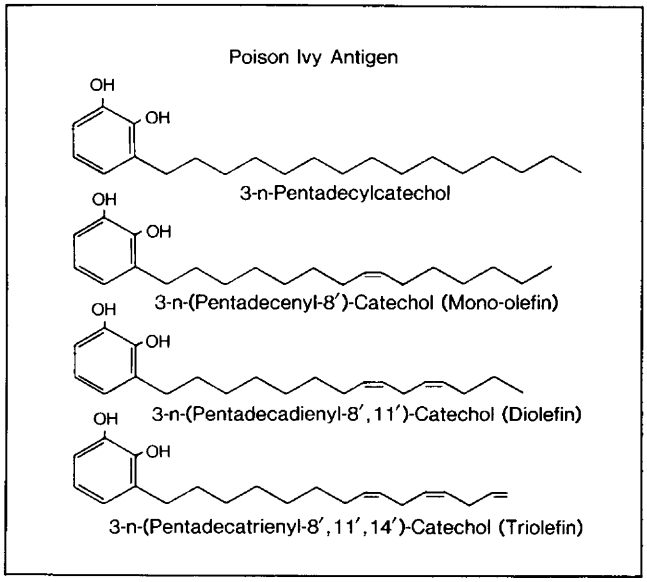

Fig 1.—Chemical structures of four pentadecylcatechols in allergenic component of poison ivy.

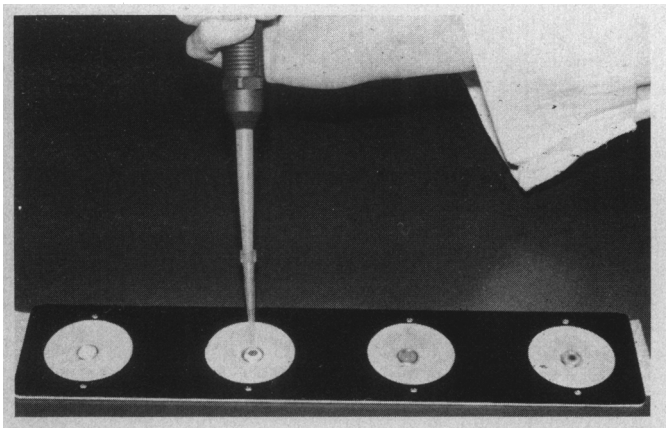

Fig 2.—Plastic template used to delineate area to which protectant was applied.

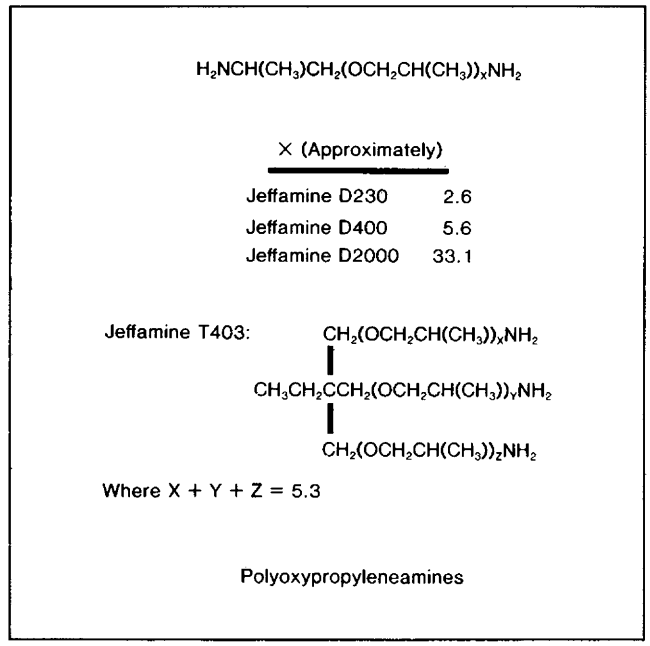

Fig 3.—Chemical formulas of Jeffamine polyoxypropyleneamines.

This work, of course, is not applicable to the millions of people who have already become allergic to poison oak and poison ivy. For them, a second approach, such as hyposensitization, is necessary. Hyposensitization refers to the reduction of existing sensitivity. Epstein et al[9,10] have also shown that this can be accomplished, but it requires large doses (in the range of 300 mg of urushiol) to be ingested over a long period of time. Maximal hyposensitization requires three to six months to develop and tends to diminish once administration of the antigen is stopped. Side effects such as pruritus ani and skin rashes are common during treatment. In addition, there have been rare reports of renal complications in patients receiving poison ivy extracts for hyposensitization.[11] The association of the renal disease and the hyposensitization in these reports, however, is largely circumstantial and has not been confirmed. Because of the problems involved, most dermatologists attempt oral hyposensitization only in extremely sensitive individuals when heavy exposure is unavoidable.

A third approach is the application of a protective substance to exposed skin before exposure to the antigen. This approach has been investigated for over 40 years using substances as varied as exchange resins,[12] tyrosinase,[13] sodium perborate,[14] chloramide,[15] zirconium salts,[16] and alkaline peroxide.[17]

We evaluated the ability of a number of substances to protect sensitive subjects from poison oak/ivy dermatitis using a closed patch test system. Several reducing agents were evaluated in an effort to see if oxidation of the catechols to the more reactive quinone could be prevented. Several simple nucleophiles (substances that contain an unshared pair of electrons and thus are attracted to the partial positive charge of the quinone) were also evaluated. They were chosen to establish whether providing a more readily available substance for the catechol or quinone to react with on the skin surface could prevent formation of the complete antigen within the skin. This assumes that the product that is formed cannot penetrate the skin and/or is nonallergenic. Along the same line of thinking, we also investigated polyvinylpyrrolidone (PVP) and some of its derivatives, since they are known to react with quinones.[18] Finally, we investigated the usefulness of a dimer of linoleic acid and several linoleic acid dimer salts. Most of the dimer salts consisted of the linoleic acid dimer and a polyamine. We selected these substances because the addition of linoleic acid dimer salts to cutting oils has been remarkably successful in decreasing the incidence and severity of irritant dermatitis in machinists,[19] and previous preliminary work suggested that they might also be useful in diminishing allergic contact dermatitis.

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MATERIALS AND METHODS

All patch testing was performed on the back of volunteers using 1-mm-diameter aluminum chambers (Finn) and hypoallergenic tape (Scanpor). A plastic template was designed to define the area to which a given protective agent was applied. The template had four circles placed in a linear arrangement, with the center of two adjacent circles being 7.5 cm apart and each circle having a diameter of 4 cm (Fig 2). The poison ivy extract used was purchased as a crude poison ivy resin (Hollister-Stier Laboratories) after it was determined with gas chromatographic analysis that it contained 27 mg of urushiol per gram of resin. Appropriate ethanolic dilutions were made and stored at 6°C.

We used Jeffamine (polyamine) compounds D400, D230, D2000, and T403. Their chemical structures are given in Fig 3. The numerical portion of the name refers to the approximate molecular weight, the alphabetical portion refers to whether the substance is a polyoxypropylene diamine (D) or triamine (T).

Preparation of Dimer Salts

The various polyamine salts of linoleic acid dimer (hereafter to be called *dimer salts*) were prepared in our laboratory by first mixing various ratios of the pure polyamine with the linoleic acid dimer to form a gel. These salts were subsequently added to different vehicles in the concentrations listed. An example of the formula for the standard dimer salt Jeffamine D400 (1:1) is 10.3% linoleic acid dimer, 14.7% Jeffamine D400, and 75% distilled water. Other formulas were also prepared in which the proportion of polyamine to linoleic acid dimer was doubled (2:1) or increased by sixfold (6:1).

Determination of Sensitivity

Seventy-seven paid volunteers who were allergic to poison ivy/oak were evaluated after obtaining approval from our human experimentation committee and securing appropriate informed consent. The volunteers were mostly students and employees at the Oregon Health Sciences University, Portland, whose ages ranged from 21 to 61 years (mean age, 31 years). Each individual underwent closed patch testing to six different dilutions of the poison ivy extract (ranging from 0.02 to 5.0 μg of catechol equivalent in twofold dilutions) to verify their allergy to poison ivy and to determine the severity of their allergy. Testing was performed using 5 μL of antigen placed on a filter paper disk (8 mm in diameter). The center of each disk was a minimum of 7 cm away from the center of any other disk. All testing was performed on the back, with occlusion, for 48 hours. After 48 hours, the tape was removed and discarded, and the sites were read five to 15 minutes later. The sites were read again seven days after placement of the patches. Sites were graded according to the following criteria used by the North American Contact Dermatitis Group: 1 equals a weak reaction (erythema only); 2, a strong reaction (edematous or vesicular); 3, an extreme reaction (spreading or bullous); 4, a doubtful reaction; 5, an irritant reaction; and 6, a negative reaction. (*Patch Testing in Allergic Contact Dermatitis*, ed 6, 1982. Prepared by the North American Contact Dermatitis group in conjunction with the American Academy of Dermatology and Hermal Pharmaceutical laboratories.) Twenty subjects did not give a grade 2 reaction to at least one strength of the extract, so they were excluded from further testing. Of the remaining 57 subjects, 47 elected to proceed with further testing.

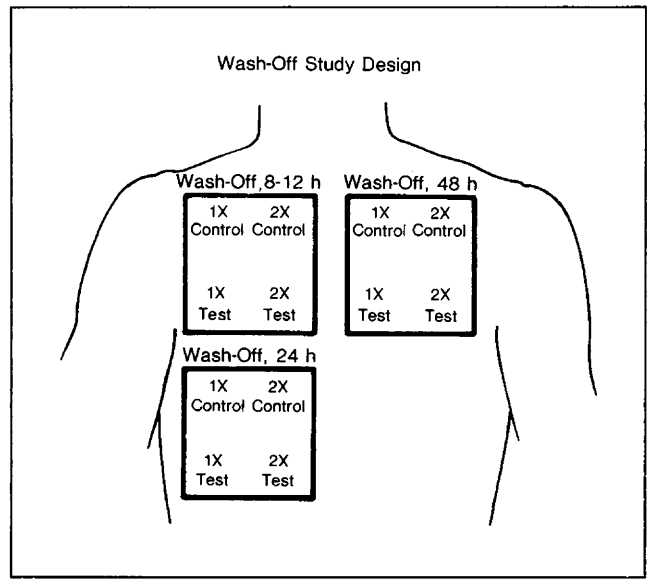

Fig 4.—Diagram of wash-off study design.

Evaluation of Protective Substances

Three or more weeks after the sensitivity testing had been completed, the subjects were brought back. At that time, each subject had 16 sites (one "panel") marked on the back using a special template. The template (see "Materials and Methods" section) consisted of a 29.5 × 6.5-cm strip of firm, but flexible, plastic (Fig 2). The spacing was designed to minimize the nonspecific irritability of the skin known as the *angry back* or *excited skin phenomenon*.[20,21] A thin layer of different protective substances (approximately 40 to 60 mg of protectants in liquid vehicles, or 40 to 70 mg of protectants in petrolatum vehicles) were applied to each 4-cm-diameter site using a cotton swab. One site was always left unprotected to act as the antigen control. After allowing the protectants to dry for about ten minutes, the sites were challenged with 5 μL of poison ivy extract using our closed patch test system. Each extract-impregnated disc was placed approximately in the center of the "protected" areas. The concentration of antigen used was determined individually, based on the data from the initial sensitivity test. The lowest concentration that gave a grade 2 reaction was always chosen as the test concentration. This concentration generally elicited a reproducible degree of dermatitis, in which even partial protection from a dermatitis could be demonstrated by a decrease in the dermatitis to a grade 1 reaction, while still minimizing the participant's discomfort as much as possible.

As before, the tape was removed after 48 hours, and readings were performed at 48 hours and seven days. Reactions were graded according to the criteria mentioned above. A minimum of three weeks passed from the end of one panel to the beginning of another panel as another means of minimizing the angry back phenomenon.

Wash-Off Trial

In this phase of the study, the back was divided into three sections (Fig 4). One section, consisting of four sites, was the eight- to 12-hour region; a second section, also consisting of four sites was the 24-hour region; and the third section, consisting of eight sites, was the 48-hour region.

The following tests were performed in each section: site

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Table 1.—Protective Effect of Linoleic Acid Dimer and Its Derivatives

	Petrolatum Base, %						Ethanol Base, %					
	10		20		35		10		20		35	
Agent	N*	%*	N	%	N	%	N	%	N	%	N	%
Linoleic acid dimer	10	10	...	...	7	0	10	0	...	...	5	0
Bishydroxyethyldimerate	10	0	...	...	9	11	10	0	...	...	8	12
Dimer salt Jeffamine D400	11	9	11	27	16	69	10	10	10	50	10	30
Dimer salt Jeffamine D400 (2:1†)	10	30	10	10	10	50	10	0	9	22	11	36
Dimer salt Jeffamine D400 (6:1†)	9	33	12	42	10	50	10	10	10	30	11	36
Dimer salt Jeffamine D230	9	22	11	45	15	73	10	30	10	30	16	56
Dimer salt Jeffamine D2000	8	13	10	30	15	46	2	0	10	10	11	27
Dimer salt Jeffamine T403	10	30	16	44	17	71	12	17	15	40	15	33

*N indicates total number of subjects tested; percent sign, percentage of subjects totally protected from dermatitis.
†Indicates ratio of polyamine to linoleic acid dimer.

1, antigen control—1× (the lowest concentration of the poison ivy extract that gave a grade 2 reaction); site 2, protectant challenged by the same concentration of antigen used at site 1; site 3, antigen control—2× (double the concentration of poison ivy extract used at site 1); and site 4, protectant challenged by the same concentration of antigen used at site 3. The extra four sites in the 48-hour area were used for the routine evaluation of other protective substances. The disks and tape in the eight- to 12-hour and 24-hour areas were removed after the appropriate time interval, and the sites were washed with any available toilet soap, then rinsed with water. Generally, the subject did the eight- to 12-hour wash, himself, at home; whereas, we performed the 24-hour wash.

Mixing Experiment

In this phase, a protectant, dimer salt Jeffamine D230, 35% in ethanol, was fixed with the antigen at three different time intervals (15 minutes, two hours, and 24 hours) prior to placing them on the volunteer's back. In addition, the ratio of the protectant to the antigen was varied at each time interval (protectant-to-antigen ratios of 15:1, 5:1, 1:1, and 1:5). The 1:1 ratio represented the amount of each agent normally used in the screening evaluations. The antigen, alone, was included as a control. The patches were left on the skin for 48 hours and read at 48 hours and seven days, as usual.

RESULTS

Preliminary Trials

A total of 82 evaluation panels and 38 wash-off panels were performed on a total of 47 people. Test panels performed using reducing agents and nucleophiles (cysteamine, sodium bisulfite, glutathione, hypotaurine, cysteine, and n-palmityl cysteamine) in ethanol, polyethylene glycol, or aquaphor at concentrations of 5% to 20% showed essentially no protection. Lack of protection was also seen with PVP and and its quaternium ammonium polymers (Gafquat 734 and Gafquat 755N).

Linoleic Acid Dimer Compounds

Table 1 summarizes some of our results using linoleic acid dimer (Empol 1010), bishydroxyethyl dimerate (Emery 9360-A), and four polyoxypropyleneamine salts of the linoleic acid dimer (dimer salts). The linoleic acid dimer, by itself, and its bishydroxyethyl derivative provided little benefit. However, a significant decrease in the number of subjects with a dermatitis was seen when the linoleic acid dimer was modified by the addition of various polyamines to make different dimer salts. For example, three of the dimer salts—Jeffamine D400, Jeffamine D230, and Jeffamine T403—each at 35% concentrations in petrolatum, totally protected approximately 70% of the 15 to 17 subjects tested.

Table 2.—Efficacy of Polyoxypropyleneamines, Alone, as Protectants

	In Ethanol, %				In Petrolatum, %			
	20		35		20		35	
Agent	N*	%*	N	%	N	%	N	%
Jeffamine D400	10	10	9	11	17	41†	9	11
Jeffamine D230	8	25	8	13	8	0	...	...
Jeffamine D2000	5	0	4	25	5	0	6	50‡

*N indicates total number of subjects tested; percent sign, percentage of subjects totally protected from dermatitis.
†Three were unprotected when rechallenged.
‡Irritation from the "protectant" was evident; 30% concentration was used, not 35%.

There was no consistent difference in the protection provided based on the vehicles we used: at times, the petrolatum base was better; whereas, at other times, the ethanol base was superior. There is, however, a definite trend of improved ability to protect with increasing concentrations of the dimer salt. A 5% concentration (not listed) is essentially nonprotective; whereas, the 10% preparations protected 0% to 33% of the subjects tested, and the 35% preparations protected 27% to 73% of the subjects.

When the proportion of the amine to the linoleic acid dimer was increased, as with the dimer salt Jeffamine D400 (2:1) and the dimer salt Jeffamine D400 (6:1), consistent improvement in protection was noted. This suggested that the amine was not reacting chemically with the poison ivy pentadecylcatechols, in which case a concentration-dependent

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Table 3.—Wash-Off Trials

Agent	Usual Challenge Dose, h						Challenge Dose Doubled, h					
	8-12		24		48		8-12		24		48	
	N*	%*	N	%	N	%	N	%	N	%	N	%
Dimer salt Jeffamine D400, 35% in petrolatum	15	93	15	60	15	40	15	100	15	53	15	40
Dimer salt Jeffamine D400, 35% in ethanol	10	80	10	50	10	30	10	70	10	20	10	10
Dimer salt Jeffamine D400, 50% in water	9	78	9	67	9	44	9	56	9	22	9	22
Dimer salt Jeffamine D230, 35% in petrolatum	10	90	10	80	10	40	10	90	10	60	10	20
Jeffamine D400 (not dimer salt), 20% in petrolatum†	7	43	7	14	7	0	7	0	7	0	7	14

*N indicates total number of subjects tested; percent sign, percentage of subjects totally protected from dermatitis.
†Significant irritant reactions to protectant were seen in five of seven subjects.

Table 4.—Mixing Experiment

Ratio of Protectant to Antigen	No. (%)*		
	15 min†	2 h†	24 h†
15:1	8 (88)	8 (100)	8 (100)
5:1	7 (71)	7 (86)	7 (57)
1:1	8 (37)	8 (25)	8 (50)
1:5	7 (0)	7 (14)	7 (0)

*No. indicates total number of subjects tested; percent sign, percentage of subjects totally protected from dermatitis.
†Time interval between mixing protectant, dimer salt Jeffamine D230 (35% in ethanol), and poison ivy resin.

benefit could have been expected.

The polyamines are a necessary component of the preparations, but they are not sufficient by themselves. This is readily seen in Table 2 where the polyamines are used without the linoleic acid dimer. In only two instances was protection greater than 25% obtained. In one of these cases (Jeffamine D2000, 35% in petrolatum), irritation was a significant problem that limited the usefulness of the preparation. In the other instance (Jeffamine D400, 20% in petrolatum), 41% of the subjects were protected. However, this result was not consistent with the other preparations. In addition, three of nine subjects who were protected originally were not protected when rechallenged later. Thus, the validity of the original results are questionable.

Wash-Off Trial

This test was performed to see if the protection provided by a given agent could be improved by washing off the protectant and the antigen before the usual 48-hour reading. The amount of antigen used as a challenge was also doubled to see if the amount of protection provided was readily overcome. In all but one case, the control sites exhibited a dermatitis. As can be seen in Table 3, when dimer salt Jeffamine D400, 35% in petrolatum, was used as the protectant, more than 90% of the 15 subjects tested were totally protected from a dermatitis. This was seen at both doses of the antigen if the sites were washed off within eight to 12 hours after application. If one waited until 24 hours to wash off the sites, only 60% of the subjects were protected from the usual challenge dose of antigen (53% protected with double the dose of antigen). When the sites remained occluded for the full 48 hours, protection dropped to 40%.

The same trend was seen with the other dimer salts; total protection of 78% to 90% of subjects was obtained with the eight- to 12-hour wash-off. This dropped to 30% to 44% with the longer exposure times. The results were even more striking when the challenging dose of antigen was increased, since 56% to 90% of subjects were totally protected from a dermatitis with an eight- to 12-hour wash-off; whereas, only 10% to 22% of subjects were protected when the antigen and the protectant were left on for 48 hours.

The Jeffamine D400 polyoxypropyleneamine, 20% in petrolatum (without the linoleic acid dimer), was evaluated in a similar manner, to determine whether the protective effect could be obtained with the polyamine alone or was dependent on the combination. In the seven subjects tested, there was negligible protection with one exception; 43% of the subjects were protected from the routine dose of antigen with an eight- to 12-hour wash-off. This effect was not seen when the dose of antigen was doubled, so its significance is uncertain. In addition, five of seven subjects showed significant irritant reactions in the area of the protectant, which had not been seen with the dimer salt preparations and which would severely limit any potential usefulness of the polyamine by itself.

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Mixing Experiment

This phase of the study was performed to try to determine whether the protectant was acting by chemically reacting with the pentadecylcatechol or by simply acting as a physical barrier. If the protectant were acting chemically and the reaction were not instantaneous, one would expect the protective effect to be better when the antigen and protectant were mixed together 24 hours prior to patching. If the protectant were acting as a physical barrier, it might not be as effective when the two substances are mixed together prior to application, and the protective effect might be more sensitive to the ratio of the two substances. A chemically active protectant should be less sensitive to the ratio of the two ingredients, especially with increased contact time prior to patching.

Table 4 shows that there is essentially total protection when the ratio of the protectant to antigen is highest (15:1), regardless of the time interval involved. There is essentially no protection at the lowest ratio (1:5), again regardless of the time interval. At the intermediate ratios, there is a moderate amount of protection, which is greater at the higher protectant ratio. When the time interval is considered, there is no difference in protection at the extreme ratios (15:1 and 1:5). At the intermediate ratios, there are no consistent differences between a 15-minute or 24-hour mixing interval.

These results indicate that concentration is the critical element in determining protection from dermatitis. This is most consistent with the hypothesis that the protectant acts as a physical barrier rather than by chemically altering the antigen, although it is not definitive.

Controls

An unprotected antigen control was performed with each test panel to verify the subject's reactivity and for comparison purposes. In addition, vehicle controls with plain petrolatum, ethanol, and water were performed on nine to 10 volunteers each. In no case did they diminish the dermatitis when compared with the simultaneous unprotected antigen controls.

COMMENT

We have presented a method that we have found to be a rapid, efficient means of evaluating a large number of potential protectants in varying vehicles and concentrations. In general, there was little discomfort to subjects. In no instance did a subject develop a widespread or serious reaction. This may be because the dose of challenge antigen was individually tailored to match the subject's degree of sensitivity. Individualized selection of the antigen challenge dose, along with wide spacing of the test sites, also helped us to avoid major problems with the angry back or excited skin syndrome. Our only significant complication occurred early in the study when we chose a previously unknown, potent sensitizer (2-n-decylaminoethanethiol) as a potential protectant.[22] Two of three subjects exposed to this chemical became sensitized. This chemical was quickly removed from the study, and there have been no sequelae associated with the sensitizations.

The simple chemical nucleophiles and the PVP compounds were not protective in the concentrations used. We recognized that the nucleophile concentrations were much lower than those used with the linoleic acid dimer salts, but little, if any, benefit was noted, even at the day 2 reading, so it was felt that further testing in this area would not be profitable. We also experienced great difficulty in obtaining a homogeneous mixture of the nucleophilic substances, even with the concentrations tested.

The polyamine salts of linoleic acid dimer (eg, dimer salts) have demonstrated total ability to prevent poison oak/ivy dermatitis in some people. This is despite the following factors, which bias the results against the effectiveness of the protectants: (1) occlusion, which enhances penetration of the antigen; (2) application of the antigen for 48 hours, which is much longer than the usual clinical situation; and (3) dermatitis from the simultaneous testing of multiple agents producing an increased likelihood of nonspecific irritability (the angry back phenomenon). Thus, protectants that totally prevent a dermatitis in closed patch test trials are effective under very adverse conditions. When the test conditions are not as strenuous, as in the eight-to 12-hour portion of the wash-off study, which more closely simulates the usual clinical exposure, several of the dimer salts are able to prevent dermatitis in a range of 56% to 100% of subjects, depending on the preparation used.

The wash-off study results suggest that the dimer salts are acting as a physical barrier in contrast to acting by chemically altering the antigens. A slow "leakage" of antigen across the barrier would account for the increasing incidence of dermatitis when the protectant and antigen are left on the skin for longer periods of time. This is also suggested by the mixing experiment, in which the concentration of the protectant was much more critical to the protection than was the interval of contact prior to patching.

There is a discrepancy between the 69% of subjects protected during our initial panels with the dimer salt Jeffamine D400 and the 40% of subjects protected with the same agent during the 48-hour portion of the wash-off trials (see Tables 1 and 3). This may be due to the small numbers of subjects tested and to the vicissitudes of a biological system. The true value probably lies somewhere between the two values.

Much remains to be done. We need to test larger numbers of subjects, to test other concentrations and different formulations of the linoleic acid dimer and polyamine salts, to determine the degree of protection offered (defined both in clinical field trials and by using higher levels of antigen in our test system), and to develop toxicity studies. The preparations we have evaluated are in very simple vehicles, and

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currently they are tacky and unpleasant. Thus, cosmetically acceptable formulations need to be developed and then tested to assure that they maintain their efficacy. However, the results obtained so far are encouraging and will hopefully result in products that will be able to prevent poison ivy/oak dermatitis in the population at risk.

This project was supported in part by grant BSRG S07 RR05412, awarded by the Biomedical Research Support Grant Program of the Oregon Health Sciences University. Additional support was obtained from the National Institutes for Occupational Safety and Health grant 5-R03-OH01737.

The Jeffamine compounds D400, D230, D2000, and T403 were kindly supplied by the Texaco Chemical Co, Bellaire, Tex; the linoleic acid dimer Empol 1010 and the bishydroxyethyl dimerate, by Emery Industries, Cincinnati; and the polyvinylpyrrolidone and its quaternium ammonium polymers Gafquat 734 and Gafquat 755N, by the GAF Corp, Wayne, NJ. The other chemicals used (cysteamine, sodium bisulfite, glutathione, hypotaurine, and cysteine) were purchased through either the Sigma Chemical Co, St Louis, or the Aldrich Chemical Co, Milwaukee, with the exception of the *n*-palmityl cysteamine, which we synthesized.

We would like to thank our devoted volunteers for their participation. In addition, we would like to acknowledge Robert Adams, MD, Harvey Blank, MD, and the Cincinnati-Milacron Co for their assistance in the selection of some of the test chemicals, and Connie Strawn for her technical assistance.

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