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Allergic contact dermatitis due to nonylphenol ethoxylate (Nonoxynol-6)*

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The non-ionic emulsifier "nonoxynol-6" found in an industrial waterless hand cleanser induced allergic contact dermatitis on the upper extremities of a uranium mill maintenance worker. The chemical is an irritant for the rabbit. It was not shown to be a cutaneous sensitizer for the albino guinea pig using the guinea pig maximization test.

Key words: Contact dermatitis – surfactant – emulsifier – detergent – waterless hand cleanser – nonoxynol – uranium mill workers.

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Dermatitis in patients exposed to surfactants or emulsifiers has traditionally been considered to result from irritation (1) rather than allergy, though instances of sensitization to lauryl ether sulfate (LES) have been reported (2–5). Sodium lauryl sulfate (SLS) has also been shown to cause allergic contact eczema (6–8), as has the "Tego" group of emulsifiers (9).

The purpose of this article is to report a case of contact dermatitis due to the non-ionic emulsifier nonylphenol polyethoxylate-6 or "nonoxynol-6" (N-6) and to present data pertaining to its irritant and sensitization potential in animals.

Report of the Case

A 58-year-old uranium mill maintenance worker developed scaling, redness, vesiculation and fissuring of the dorsal hands and forearms associated with a transverse dystrophy of his fingernails. This became so severe after 3 months, that he was unable to work. It was noted that when he returned to work, within 2 to 3 days, his skin condition deteriorated. While off work, the eruption subsided in 7 to 10 days.

Material and Methods

Patch testing

Patch tests were performed using "Al Test" Strips (Hollister-Stier Ltd., Toronto) occluded with "Scanpor" tape (Hollister-Stier Ltd., Toronto). The strips were affixed to the upper back. They were removed at 48 h and the sites were examined after all "dimpling" of the skin due to the pressure of the filter paper discs had resolved: between 30–45 min. The sites were scored using the scoring system recommended by the International Contact Dermatitis Group (11).

Patch tests were performed first with the European Standard Screening Test Series of chemicals (Trolab, Copenhagen, Denmark). Several weeks later, the patient was patch tested with the chemicals listed in Table 1 at their

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Table 1. Waterless hand cleanser components used for patch tests and their respective concentrations (in gm% w/w); all were in pet. except perfume where olive oil was used

quaternium 15	2%
propylene glycol	10%
nonoxynol-6	0.5%
octoxynol-9	0.5%
lanolin	100%
technical white mineral oil	100%
butylated hydroxytoluene	2%
perfume	10%

respective concentrations as noted. The patient had no active skin lesions at the time of these tests. The latter group of chemicals are the constituents of a waterless hand cleanser which the patient used at work. There was no reaction to N-6 at 0.5% concentration in pet. in 8 human subjects tested as controls. Fisher (12) has suggested a concentration of 5% in pet. ten times the concentration utilized in this instance, as an appropriate topical concentration for patch tests with this class of chemicals. The lack of response in the 8 control subjects combined with the low concentration utilized compared to what has been recommended by Fisher, suggests that the 0.5 gm% (w/w) is a subirritant concentration appropriate for the demonstration of contact allergy.

Animal investigations

Irritancy. 6 New Zealand white rabbits were purchased from the Guelph Rabbitry, Guelph, Canada. The animals' backs were clipped using an Oster Small Animal Clipper (Oster Corporation, USA). 3 emulsifiers which were condensation products of ethylene oxide, including the N-6 in our patient's waterless hand cleanser and 2 other similar emulsifiers supplied by manufacturers of 2 other waterless hand cleansers, were applied to the rabbits under "Al Test" strips in the concentrations noted in Table 2. The strips were placed 2 cm apart and were affixed to the animals' skin with Scanpor tape. Elastoplast bandage (Smith and Nephew Ltd., Toronto) was wrapped around the animals' torsos to secure the patches in place. The bandages were removed after 24 h and the sites were scored for the presence or absence of irritation at each topical concentration after 48 h. No endeavour was made to score the individual irritant reactions beyond deciding whether the skin was irritated or not.

The animals were housed in metal cages and allowed fresh water and Purina rabbit chow *ad libitum.*

Sensitization. The guinea pig maximization test (GMT) as described by Magnusson & Kligman (12) was employed. 20 albino Hartley-Dalkin strain guinea pigs weighing 300–500 g, purchased from the Connaught Laboratories, Toronto, Canada, were utilized, 5 animals at each of the 4 concentrations. 10 similar control animals were used initially, which established a non-irritant topical concentration of 2.7% in pet. for subsequent challenge patch testing. The highest intradermal concentration that could be injected without sloughing of the skin or intoxication of the animals, 27 gm%, was administered in propylene glycol to 5 animals, and 3 lower concentrations, 9, 3 and 1.7 gm%, were each administered to the 3 separate groups of 5 animals, respectively.

On day 1, the animals received 3 pairs of injections of the following chemicals in the shoulder region:

(i) 0.1 cc of N-6;

(ii) 0.1 cc of N-6 mixed with Freund's complete adjuvant (FCA) (Difco Laboratories, Detroit Michigan, USA) mixed 50:50;

(iii) 0.1 cc of FCA.

Table 2. % of rabbits irritated by waterless hand cleanser emulsifiers

	% of animals reacting at each topical concentration (gm% (w/w) in pet.) $N=6$			
Chemical	25%	50%	75%	100%
nonoxynol-6	66.7	66.7	66.7	83.3
emulsifier (A)	33.3	50.0	50.0	66.7
emulsifier (B)	0	16.7	16.7	16.7

On day 7, N-6 was applied over the sites of the injection, after shaving the area, at a concentration of 100% under a 2 cm×4 cm Whatman 3MM filter paper occluded with Blenderm (3M Company, USA), and the patches were secured with 7.5 cm Elastoplast (Smith and Nephew Co., Toronto) wrapped firmly around the animals. These bandages were removed at 48 h.

On day 21, the animals' flanks were shaved and 2.7% N-6 in pet. was applied to the animals' flanks on a single Al test strip disc occluded with Scanpor tape. The patch tests were further secured to the animals by wrapping 7.5 cm elastoplast bandage about the animals' torsos. The patches were removed at 24 h and the sites were observed for evidence of reaction at 48 h.

Subsequently, 20 of the animals that had been exposed to deodorized kerosene and 20 exposed to tetraethylene glycol diacrylate in the GMT test were patch tested with 2.7% nonoxynol in the same fashion as above, 2 weeks after the completion of the previous experiment with the two other chemicals. This yielded a reassessment of the irritancy of N-6 in animals having been exposed to FCA in a GMT protocol but not to N-6.

Results

The proportion of animals reacting in different experimental groups was compared using binomial distribution calculations of the relative proportions and the χ^2 test (13). Relationships were taken to be significant if the chance of occurrence was less than 5%.

The patient exhibited no positive epicutaneous responses to the European Standard Patch Test Series. He had a 1+ reaction to N-6 at 48 and 96 h but no reaction to any of the other chemicals noted in Table 1. A biopsy of the patch test site was in keeping with an allergic contact reaction (14).

Table 2 summarizes the results of the irritancy assessment of N-6 and 2 other non-ionic emulsifiers used in waterless hand-based cleaners. On challenge, animals in the group receiving induction concentrations of 29, 9, 3 and 1.7 g/100 g exhibited reactions in 2/5, 1/4, 0/5 and 2/5 animals, respectively. 5 of the 40 animals in the group having been exposed to the GMT protocol with either deodorized kerosene (20 animals) or tetraethylene glycol diacrylate (20 animals) reacted to topical challenge with 2.7 g% (w/w) N-6. The proportion of responses to challenge testing in the animals exposed to N-6 and in the 40 animals not so exposed was not statistically significantly different ($Z=0.8195$, n.s.). N-6 is more irritant than emulsifier (B) when compared at 100% concentration ($\chi^2=5.3333$, $p=0.0209$). Emulsifiers (A) and (B) ($\chi^2=3.0857$, $p=0.0789$) and N-6 and emulsifier (A) ($\chi^2=1.6666$, $p=0.19670$) were not statistically significantly different from one another at 100% and 25% concentrations, respectively, which revealed the most divergence in the number of animals reacting. When the animals reacting to the highest induction concentration (i.e. 27% and 9%) were compared to the animals receiving the low induction concentration (i.e. 3% and 1.7%), there was no statistically significant difference in the proportion of animals responding to the topical challenge ($\chi^2=0.4342$, $p=0.5098$).

Discussion

The history of detergents has been summarized by Davidson & Milwidsky (15). The first synthetic emulsifiers or detergents were manufactured during the first world war and were short-chain alkyl naphthalene sulfonates made by reacting butanol or propanol with naphthalene, following which they were sulfonated. During the second world war, synthetic emulsifiers came into wider use combined with sodium salts of carboxymethylcellulose (CMC) which removed dirt and kept it in suspension, producing a good washing product for moderately dirty cleansing activities. In 1947, condensed phosphate detergents such as sodium tripolyphosphate were developed which combined with CMC gave a heavy duty wash

product without the adverse property of precipitating calcium or magnesium salts from water onto washed materials, which was associated with soaps.

Synthetic detergents may be categorized as anionic, cationic or non-ionic. Anionics such as long-chain fatty acid alcohol sulfonates are widely used in shampoos. Cationics, such as quaternary ammonium salts are used as germicides, ionic hair rinses and fabric softeners. Most non-ionic detergents are condensation products of water-soluble ethylene oxide (EO) and a hydrophobic agent such as a long-chain fatty acid, an amine or an amide. Nonoxynols are synthesized from alkylbenzene nonynol by reacting it with EO to produce EO polymers of varying chain length. N-6 contains between 4 and 6 EO sub-units.

EO not bound in ethoxylate chains during synthesis reacts with water during the chemical reaction yielding small amounts of ethylene glycol. Variation in the amount of ethylene glycol and variation in the average length of the polyethoxalate chain probably accounts for differences in the irritancy of nonoxynols. Such a difference is demonstrated between N-6 and emulsifier (B) in this investigation. Dobson (16) found that a waterless hand cleanser containing emulsifier (B) had a lower irritancy potential than other similar products in human experiments.

Nonoxynols are used as detergents, emulsifiers for creams, fabric softeners, photographic paper additives and liquid soaps, and may be found in spermicidal creams (17), hair dyes (18) and lubricating oils (19).

The GMT results with N-6 did not reveal a greater proportion of animals responding at higher or lower intradermal induction concentrations nor did more of the exposed animals react to topical challenge than the GMT-induced animals with no N-6 exposure. It is concluded that N-6 has not been shown to be a cutaneous sensitizer for the guinea pig in this small group of test animals and it probably has a low sensitization potential for this animal.

The reduction in the irritancy threshold for N-6 in the animals exposed to chemicals unrelated to it in the GMT compared with the pre-test control animals is noteworthy. None of the pre-test control animals reacted to 2.7% N-6 in pet. while 5 of the 40 GMT control animals did. This difference, though not statistically significant ($Z=1.2959$, $p=0.1$) is in keeping with the excited skin syndrome described by Maibach (20), and it emphasizes the need to use animals exposed to CFA as challenge test controls to ensure that non-specific alteration in cutaneous inflamatory response (i.e. irritation) is not confused with specific changes in response (i.e. sensitization).

The choice of 0.5% as a concentration of N-6 in pet. for patch testing seems appropriate, as none of the 8 control subjects were irritated when patch tested with this concentration, and it is one tenth of the concentration recommended by Fisher (11) for nonoxynols. The time course of the patient's response with the persistence of the cutaneous reaction at 96 h, and the histopathology of the patch test site are in keeping with allergic contact dermatitis (14). The patient avoided further exposure to the waterless hand cleanser containing N-6 for 6 months and has had no recurrence of symptoms.

This patient and one reported by Hannuksela et al (21) are the sole instances of human contact allergy due to non-ionic surfactants which have been reported to date. This lack of evidence of human skin sensitization, the inability to sensitize the guinea pig to N-6 in this investigation, and the widespread use of such chemicals within the community suggest that the practical risk of sensitization to non-ionic agents must be extremely low.

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