

Dose response relationships in allergic contact dermatitis: Glutaraldehyde-containing liquid fabric softener

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Glutaraldehyde (GTA) is an effective preservative in some consumer products. Because it is a weak cutaneous allergen at certain concentrations, studies were conducted to assess any potential hazard of adding a low level (550 ppm) of GTA to an experimental liquid fabric softener. Allergic contact dermatitis (delayed hypersensitivity) was not elicited in challenge tests of 16 GTA-sensitive subjects or in repeated insult patch tests of 706 normal human male and female subjects. The subjects were exposed (1) to the experimental formulation, (2) to the formulation with 10 times the normal level of GTA, and (3) to fabrics laundered with the normal use level or with 10 times the normal use level of these experimental formulations.

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Glutaraldehyde (GTA, pentanediol, $\text{OHC}-(\text{CH}_2)_3-\text{CHO}$) is used to preserve cosmetics and household products, to sterilize medical and dental equipment, to fix tissues for histologic examination, to treat plantar hyperhidrosis, and to tan leather (Juhlin & Hansson 1968, Meltzer & Henkin 1970, Jordan et al. 1972). The tests described herein relate to the use of GTA as a preservative in an experimental household laundry formulation. They were performed to assess any dermatologic hazard of incorporating low levels of GTA into this formulation which may come into frequent contact with the skin. Because GTA is a weak cutaneous allergen (Gordon & Mai-

bach 1969, Jordan et al. 1972, Marzulli & Maibach 1974, Sanderson & Cronin 1968), subjects known to be hypersensitive to GTA, as well as non-allergic subjects, were included in the testing program.

Materials and Methods

Test materials

The materials tested were:

1. An experimental liquid fabric softener containing 550 ppm of GTA
2. Cotton T-shirt fabrics laundered with the normal use concentration of this formulation

3. The experimental liquid fabric softener containing 10 times the normal level of GTA (5500 ppm)
4. Cotton T-shirt fabrics laundered with 10 times the normal use concentration of the formulation.

The glutaraldehyde employed in these tests was a commercially available 25 % aqueous cosmetic grade solution (Union Carbide Corporation, 270 Park Ave., New York, NY 10017).

The presence of allergic contact dermatitis in hypersensitive persons was confirmed by a 72-h occluded challenge patch test using 1 % aqueous solutions of GTA. The occlusive patches used in the several tests were either Johnson & Johnson clinical patches, or 22 mm diameter circular pads of Webril® nonwoven cotton on Blenderm® adhesive tape.

Formulations containing no GTA were used as controls and to prepare control fabrics. Appropriate controls were used in all tests and all evaluations were done blind, that is, the examiner did not know the identity of the materials applied to the sites examined.

Methods

Challenge patch tests in sensitized subjects. Two subjects known to be allergic to GTA received diagnostic 72-h occluded applications of treated cotton T-shirt fabrics under close supervision in a procedure that otherwise followed the method described by Freget (1974). These fabrics had been treated using the recommended use level and 10 times the normal use level of the experimental formula (550 ppm of GTA) in the laundry rinse water.

Challenge use tests. GTA-hypersensitive subjects were exposed under close supervision to the undiluted experimental fabric softener formulation containing 550 ppm of GTA

and to cotton T-shirts that had been laundered using it. Two male volunteers applied 1 ml of the undiluted experimental formulation to one forearm for 1 min, twice daily, for 8 consecutive days in an "open" exaggerated use test. In a closely supervised clinical wearing test, 14 GTA-hypersensitive male subjects wore cotton T-shirts treated with the recommended use concentration of the laundry additive. The T-shirts were worn 24 h each day for 14 consecutive days. Clean T-shirts were provided daily.

Predictive delayed hypersensitivity (Draize) tests. Repeated insult patch tests were performed employing methods similar to those of Draize (1959), Marzulli & Maibach (1974) and Voss (1958). The human volunteers (706, male and female) who were not hypersensitive to GTA received nine or ten 24-h occluded patches over a 3-week induction period. Single 24-h or 48-h challenge patches were applied approximately 2 weeks after application of the final induction patch. The test materials were the experimental formulation that contained 5500 ppm of GTA and the formulation that contained 550 ppm of GTA.

Results

Challenge patch tests

No delayed hypersensitivity reactions were produced in the two GTA-hypersensitive subjects who were challenged with 72-h occluded applications of fabrics laundered using the experimental fabric softener at its normal use level and at 10 times this use level. When the concentration of GTA in the softener was 550 ppm, the levels of GTA in the rinse water were 0.4 ppm (1 times use level) and 4.0 ppm (10 times use level).

Challenge use tests

Twice-daily application of the undiluted

fabric softener (550 ppm of GTA) to the inner aspect of the lower arms of two subjects hypersensitive to GTA produced no signs of cutaneous allergy.

Daily wearing of cotton T-shirts laundered using the laundry additive (550 ppm of GTA) at its normal use level (0.4 ppm of GTA in the wash water) evoked no dermatoses among 14 GTA-hypersensitive male subjects.

Predictive delayed hypersensitivity (Draize) tests

No cutaneous allergy was induced in two separate repeated-insult patch tests of 4 % aqueous solutions of the experimental formula that contained 5500 ppm of GTA. The test solutions applied to the occlusive test patches contained 220 ppm of GTA. The test materials were applied to the interscapular areas on 340 male subjects. Two additional repeated-insult patch tests of 4 % aqueous laundry additive (550 ppm of GTA in the formulation; 22 ppm as applied to the patches) similarly produced no allergic contact dermatitis in 366 additional male and female subjects. Applications in these latter tests were to the outer aspect of the upper arm.

Discussion

GTA is available commercially in 25 % and 50 % aqueous solution. Our tests involved formulations made from the 25 % aqueous GTA.

In 50 % aqueous solution, GTA is subject to polymerization. To prevent excessive polymerization, stabilizing agents are usually added. In contrast, polymerization is less likely with the 25 % aqueous GTA commercial product and stabilizers are not required. Any possible effects of the stabilizers or polymerization upon the allergenic properties of the 50 % GTA product as compared to the 25 % product used in our tests are unknown. It is inappropriate to ap-

ply our findings to formulations that have been prepared from the 50 % aqueous GTA unless the allergenic equivalence of these GTA solutions is established.

The GTA-sensitized subjects studied had been sensitized previously in a Draize test (Marzulli & Maibach 1974) using a significantly higher concentration of GTA than is present in the undiluted experimental fabric softener liquid. Most predictive testing logistically is limited to small numbers of subjects. To allow for the theoretically greater variation in reactivity in larger populations, occlusive patches and exaggerated test concentrations were employed. These are added "safety factors".

The GTA concentration (1 %; 10,000 ppm) used in ascertaining that the subjects were patch test sensitive was 18.2 times the exposure concentration that would be encountered from the undiluted experimental fabric softener liquid and 25,000 times the concentration at recommended use levels. These solutions were freshly prepared to avoid the possibility of polymerization. Previous studies (Marzulli & Maibach 1974) demonstrated that 1 % aqueous is a non-irritating patch test concentration.

At issue is not whether GTA can sensitize (we accept that it can), but rather what is the dose response relationship between the concentrations required to sensitize non-allergic subjects and the concentrations required to elicit allergic reactions in previously sensitized subjects. From our data it appears that open patch testing with the 550 ppm of GTA, and wearing softened T-shirts (0.4 ppm of GTA in the rinse water) next to the skin was below the threshold level of these sensitized subjects.

Human exposure to glutaraldehyde from the experimental liquid fabric softener (550 ppm of GTA) would be limited. The undiluted formula would be expected to contact the skin only through spilling small amounts of it while adding it to the wash

water, or from its misuse for purposes other than those recommended. Contact with this formula most frequently would occur in laundry rinse water containing about 0.07 % of this formula, or about 0.4 ppm of GTA.

The testing program reported has included hypersensitive, as well as normal, human subjects and involved exposure to the range of GTA levels that would be anticipated from use of the experimental formulation. Delayed hypersensitivity was not induced in the normal subjects, and allergic reactions were not elicited in the hypersensitive subjects.

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