

Allergic contact dermatitis from glutaraldehyde in health-care workers

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Glutaraldehyde is considered the disinfectant of choice for sterilizing medical and dental equipment. Unfortunately, glutaraldehyde has many toxic side-effects, including the ability to induce allergic contact dermatitis. In a 5-year study at the University of Kansas, 468 patients were patch tested to glutaraldehyde. A comparison of results was made between those employed in a health-care related field and those who were not. Health-care workers (HCWs) were more than 8× more likely to be allergic to glutaraldehyde than their non-health-care working peers (NHCWs). Statistically significant differences between HCWs and NHCWs were seen in their reactivity to glutaraldehyde, thimerosal, benzalkonium chloride and methyl methacrylate. A higher than expected co-reactivity between glutaraldehyde and formaldehyde was also noted among HCWs and NHCWs, which cannot fully be explained by concomitant exposure. Allergic contact dermatitis from glutaraldehyde often causes persistent dermatitis, which frequently forces patients to leave their jobs. Although the National Institute of Occupational Safety and Health has published guidelines for safe handling of glutaraldehyde, allergy appears to continue to rise, especially among those employed in health-care professions. Until a less sensitizing disinfectant is developed, it is in the best interest of those in health-care professions, and other professions exposed to glutaraldehyde, to heighten occupational safety standards and to improve methods of barrier protection.

Key words: glutaraldehyde; allergic contact dermatitis; health-care workers; formaldehyde; cross-sensitization; NIOSH standards; occupational; prevention. © Munksgaard, 2000.

Accepted for publication 7 February 2000

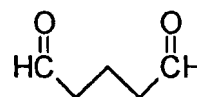
Over the past few decades, improvements in medical technology and equipment have made invasive techniques, such as endoscopy, routine. Furthermore, sterilization of instruments to eliminate the transmission of infectious disease has gained new appreciation, particularly in the era of HIV. Therefore, exposure to potentially allergic and irritant chemicals used for sterilization has become far more common than in the past. Glutaraldehyde, in particular, has been implicated as a strong irritant of the skin, eyes, and respiratory system. Repeated exposure to glutaraldehyde may also lead to the induction of sensitization, causing an allergic contact dermatitis, most often of the hands.

Currently, glutaraldehyde is recommended by the US Centers for Disease Control for cold sterilization of endoscopic equipment (1). Glutaraldehyde (Fig. 1), a saturated 5-carbon dialdehyde, is a simple organic molecule with a variety of uses in the health-care professions (Table 1). Among these, the use of glutaraldehyde is especially widespread in instrument sterilization, histologic tissue fix-

ation and radiographic development (2, 3). Glutaraldehyde's role in the sterilization of instruments stems from its ability to alkylate sulfhydryl and amino groups on organic molecules. Contaminating proteins and nucleic acids are thereby quickly denatured, accounting for glutaraldehyde's highly lethal activity against a variety of microbes including bacteria, fungi, spores, and viruses (1).

Patients and Methods

The University of Kansas is 1 of 12 participants in the North American Contact Dermatitis Group



Glutaraldehyde

Fig. 1. The molecular structure of glutaraldehyde.

(NACDG). NACDG centers conduct patch testing using standardized screening techniques and a standardized allergen tray (4). Between 1 July 1994 and 30 June 1999, patch tests were performed on 516 patients in the dermatology clinics at the University of Kansas. Prior to testing, patients completed a standardized NACDG questionnaire outlining appropriate demographic, medical and occupational information. As part of the occupational history, patients were assigned 3-digit, standardized occupational and standardized industrial codes, which specifically identify an occupation within a given industry. Subsequently, all patients were tested against a variety of potential allergens based on history, physical examination and clinical suspicion. Most patients were tested to the NACDG's standard screening tray, in addition to other allergens. From 1 July 1994 to 30 June 1996, the NACDG tray contained glutaraldehyde at 2 concentrations in petrolatum (pet.): 0.2% and 1.0%. From 1 July 1996 to 30 June 1998, glutaraldehyde was tested at 0.5% and 1.0% pet. Since 1 July 1998, the NACDG standard tray has included only 1 concentration of glutaraldehyde, 1% pet. Throughout all study periods, formaldehyde was present on the NACDG screening tray at 1% in water (aq).

Patients were patch tested in a standardized manner using Finn Chambers (Epitest Ltd, Öy, Tuusula, Finland) on Scanpor tape (Norgeplaster Aksjeselskap, Vennesia, Norway), applied to the patient's back as previously described (4). Test allergens were purchased from Chemotechnique

Diagnostics AB, Malmö, Sweden. Allergens were applied on Mondays and patients were examined at both 2 and 4 days by a staff dermatologist. Reactions were graded from 1 to 7 based on reaction morphology (Table 2). Reactions with grades of 1, 2, or 3 were considered allergic. Patients were considered allergic to glutaraldehyde and/or formaldehyde if they had a ≥ 1 reaction to the 1% concentration of the allergen.

Relevance, dermatitis site, dermatitis type, and exposure source were also determined and noted on the patient's scoring sheet. Relevance of a positive patch test reaction was graded as follows: 1 = definite: the patient was tested with a product to which he/she was exposed and that was known to contain the allergen to which he/she reacted; 2 = probable: the patient was known to have cutaneous exposure to a product known to contain the allergen to which he/she reacted; 3 = possible: the patient was likely to have cutaneous exposure to a product that was known or suspected to contain the allergen to which he/she reacted; 4 = the patient had previously had episodes of allergic contact dermatitis following exposure to the allergen to which he/she reacted; and, 5 = the relevance of the allergen could not be ascertained. In this study, only relevance scores of 1 or 2 were considered relevant.

All data were entered, retrieved and evaluated via a computer database (Access and Excel, Microsoft, USA). For comparison of data, results of health-care workers (HCWs) were subtracted from those of non-health-care workers (NHCWs) and statistical evaluation was performed by a z-test for significance of difference between 2 populations. A 2-tailed probability of $<5\%$ was taken as indication of a statistically significant difference.

Potential co-reactivity to formaldehyde was also evaluated. Patch testing to a formaldehyde solution was performed in a similar manner to that of

Table 1. Sources of glutaraldehyde exposure in health-care workers (HCWs)

instrument sterilization
embalming
tissue fixation
radiographic development
preparation of allergen and collagen extracts for injection
medical treatment of
epidermolysis bullosa
herpes simplex
hyperhidrosis
onychomycosis
warts

Table 2. Patch test morphology codes

1	weak (non-vesicular) reaction with erythema, infiltration, possibly papules
2	strong (edematous or vesicular) reaction
3	extreme (spreading bullous, ulcerative) reaction
4	macular erythema only
5	irritant morphology
6	negative reaction
7	not tested

Table 3. HCW occupations

Occupation	No. tested
registered nurses	19
nursing aides, orderlies, attendants	10
dental hygienists	5
licensed practical nurses	4
physicians	4
clinical lab technologists	3
health technologists	3
optical goods workers	2
dental assistants	1
dentists	1
dietitians	1
respiratory therapists	1
therapists, n.e.c.	1
total health care workers	55

all other allergens, including glutaraldehyde. A χ^2 test with a Yates' correction was used to evaluate data and produce the expected results for co-reactivity between formaldehyde and glutaraldehyde.

Follow-up was performed by contacting HCWs with positive allergic patch test results to glutaraldehyde. Patients were questioned about their dermatitis, including disease course following patch testing, occupational status, glove usage history, and glutaraldehyde training history.

Results

Of the 516 patients patch tested at the University of Kansas Medical Center during the study period, 468 were tested against glutaraldehyde. 55 subjects (of the 468 tested) were classified as HCWs based on their primary occupation (Table 3). Of the 55 members of the health-care sample, 51 were patch tested against glutaraldehyde. Nurses, nursing aides, dental hygienists and physicians were the most common occupations tested in our HCW sample. A demographic comparison between the HCWs and NHCWs is shown in Table 4. In general, HCWs were younger, more likely to be female, and more predisposed to atopic eczema and hay fever than were the NHCWs.

The most common allergens among HCWs are shown in Table 5. For comparison, the prevalence of allergic reactions to these allergens among NHCWs is also delineated. Statistically significant

differences between HCWs and NHCWs were seen for the incidence of allergic reactions to glutaraldehyde, thimerosal, benzalkonium chloride and methyl methacrylate. Thiuram mix also more frequently caused allergic reactions in HCWs; however, it was slightly outside the range of statistical significance. Of note, reactions to glutaraldehyde, methyl methacrylate and thiuram mix were currently relevant in the majority of patients found allergic to these allergens, while relevance for thimerosal allergy was rarely found.

The most significant results were seen with glutaraldehyde. 17 (3.6%) of the 468 subjects were allergic to glutaraldehyde. Moreover, positive reactions were more than 8× more likely in HCWs than in NHCWs. In all of the HCWs, positive reactions to glutaraldehyde were found to be currently relevant; among NHCWs, current relevance of glutaraldehyde allergy was not found in any. A demographic and clinical outline of the 9 HCWs with positive reactions to glutaraldehyde is shown in Table 6. Of those with positive allergic reactions to glutaraldehyde, additional sensitivities to colophony, thimerosal, thiuram mix and formaldehyde were common. The hands were identified as the site most frequently affected (9 out of 9), while the arms, trunk, and face were less likely involved. Of note, all 5 of the dental hygienists/assistants in our population were allergic to glutaraldehyde. Although HCWs allergic to glutaraldehyde were similar in age and sex to the HCW population

Table 4. Demographic information of the 2 groups patch tested against glutaraldehyde

	Total tested	Average age	Males (%)	Females (%)	Asthma (%)	Atopic eczema (%)	Hay fever (%)
health-care workers	51	43	18	82	12	24	27
non health-care workers	417	50	42	58	14	13	22

Table 5. Most common allergens in health-care workers (with comparison to non-health-care workers)

Allergen (concentration)	Positive HCWs	Tested HCWs	Prevalence (%)	Positive NHCWs	Tested NHCWs	Prevalence (%)	p-value
glutaraldehyde (1%)	9	51	17.6	8	417	1.9	<0.001
thimerosal (0.1%)	7	55	12.7	15	420	3.6	0.002
quaternium-15 (2%)	6	54	11.1	43	421	10.2	0.838
thiuram mix (1%)	5	55	9.1	23	423	5.4	0.054
formaldehyde (1%)	4	55	7.3	38	424	9.0	0.677
nickel sulfate (2.5%)	4	52	7.7	39	421	9.3	0.710
bacitracin (20%)	4	53	7.5	30	434	6.9	0.864
benzalkonium chloride (0.1%)	3	42	7.1	5	266	1.9	0.046
DMDM hydantoin (1%)	3	54	5.6	13	420	3.1	0.346
ethyleneurea melamine/formaldehyde (5%)	3	51	5.9	20	416	4.8	0.738
methyl methacrylate (2%)	3	54	5.6	3	418	0.7	0.003
potassium dichromate (0.25%)	3	53	5.7	12	422	2.8	0.269

HCWs: health-care workers.

NHCWs: non-health-care workers.

Table 6. Characteristics of health-care workers with allergic contact dermatitis from glutaraldehyde

Occupational description	Gender	Age (years)	History of asthma, eczema or hayfever	Site description	Other relevant allergies ^(a)	Follow up
dental hygienist	F	28	—	hand	—	NAFU ^(b)
optical goods worker	F	29	—	hand	C	NAFU ^(b)
health technologist	F	39	—	hand	—	NAFU ^(b)
nursing aide	F	43	+	arm & hand	—	patient has changed jobs due to complications of glutaraldehyde allergy and no longer has hand dermatitis; no formal training for handling glutaraldehyde was offered prior to usage.
dental assistant	F	43	—	hand	T	patient has changed jobs; the patient's hand dermatitis has resolved, however, the patient has noticed occasional dermatitis and oral irritation if she has even minimal (i.e., vapor) exposure to glutaraldehyde; no formal training for handling glutaraldehyde was offered prior to usage.
dental hygienist	F	44	—	arms, hands & trunk	B, T	patient has not changed jobs and continues to have persistent dermatitis of the hands and fingers; no formal training for handling glutaraldehyde was offered prior to usage.
dental hygienist	F	46	+	hand	BP, C, F, Q15, TM	patient has not changed jobs; patient has managed to avoid glutaraldehyde in the workplace and her hand dermatitis has resolved; no formal training for handling glutaraldehyde was offered prior to usage.
dental hygienist	M	50	—	hand & trunk	CM, F, P, T, TM	patient has changed jobs and no longer suffers from hand dermatitis; no formal training for handling glutaraldehyde was offered prior to usage.
licensed practical nurse	F	51	—	hand	—	patient has not changed jobs and continues to have persistent dermatitis of the hands and fingers; no formal training for handling glutaraldehyde was offered prior to usage.

^(a) B: bacitracin; BP: benzoyl peroxide; CM: carba mix; C: colophony; F: formaldehyde; P: p-phenylenediamine; Q15: quaternium-15; T: thimerosal; TM: thiuram mix.

^(b) NAFU: not available for follow-up.

studied, atopic dermatitis was significantly under reported in the glutaraldehyde affected group compared to the HCW group as a whole.

In the follow-up stage of our study, 6 of 9 HCWs with positive patch tests to glutaraldehyde were contacted and questioned (Table 6). 3 had changed jobs and reported resolution of their dermatitis. Of the remaining 3 HCWs who had not changed occupations, 2 still suffered from the dermatitis. The other HCW now avoids glutaraldehyde while on the job and no longer suffers from contact dermatitis. Furthermore, none of the interviewed HCWs reported any formal training prior to using glutaraldehyde, nor were specialized gloves made available for handling glutaraldehyde.

Discussion

A review of the literature (Table 7) reveals occasional case reports and patch test studies of

glutaraldehyde-induced allergic contact dermatitis since the Sanderson & Cronin (5) initial report. In these reports, HCWs and janitorial employees have been most frequently cited as occupations with high degrees of sensitization to glutaraldehyde, while non-occupational exposure to cosmetics (3), hair-care products (17), and fabric softeners (18) have also been reported to induce sensitization.

In a 1998 study by Kiec-Swierczynska et al. (15) of 280 HCWs at the Nofer Institute in Poland suffering from skin lesions, 12.4% were found to be allergic to glutaraldehyde. Glutaraldehyde sensitization was highest among nurses, physicians and dental assistants, with rates of 16.5%, 13.5% and 33.3%, respectively. Furthermore, the incidence of such sensitivity appears to have risen over the past decade. At the Nofer Institute in Poland, only 1 case of glutaraldehyde sensitivity was seen prior to 1993, while an average of 11 cases per year has recently become the norm (15). In collective data

Table 7. Selected case reports/studies of glutaraldehyde allergic contact dermatitis in health-care workers

Reference	Description
(5)	2 nurses were exposed to glutaraldehyde during instrument sterilization; both patients displayed positive patch test results to 1% aq. glutaraldehyde and negative results to 2% formaldehyde
(6)	a female dental assistant was exposed to 2% aq. glutaraldehyde disinfectant solution; she developed a rash on her fingers and hands that eventually spread to cover her arms and legs; patch test results showed a positive reaction to glutaraldehyde and a negative reaction to 2% aq. formaldehyde
(7)	3 dental assistants developed allergic contact dermatitis on the dorsal surfaces of the hands; patch testing with 0.25% and 1% aq. glutaraldehyde were positive, while 2.5% aq. formaldehyde was negative
(8)	a female intensive care unit nurse was exposed to glutaraldehyde and benzalkonium chloride while disinfecting respirators; she also used rubber gloves; she developed eczema on both hands. Patch tests were positive to 1% aq. glutaraldehyde and the rubber glove
(9)	2 nursing aides developed a vesicular dermatitis of their hands and forearms after handling endoscopic disinfectants; both patients were positive to 1% glutaraldehyde and negative to 2% aq. formaldehyde; in one case, the dermatitis resolved following termination of the job, while, in the other case, the dermatitis persisted
(10)	a surgical instrument nurse and a gastrointestinal endoscopic nurse both developed an allergic contact dermatitis following the use of a glutaraldehyde disinfectant; patch testing to the disinfectant was positive in both cases
(11)	13 workers with glutaraldehyde-induced occupational contact dermatitis were followed between 1981 and 1987; hand dermatitis was the presenting complaint in all cases; patch testing to 1% glutaraldehyde was performed; 9 patients showed positive reactions at both 30–60 min and at 96 h, while the other 4 patients showed positive reactions at 96 h; 3 patients were also sensitive to formaldehyde; follow-up confirmed a persistent dermatitis in 8 of the cases and a change in occupation in 5 of the cases
(2)	a respiratory therapy department worker developed an allergic contact dermatitis of her hands, arms, face and neck after using a 2% glutaraldehyde solution; patch testing to 1% aq. glutaraldehyde was positive at 48 hours, while all other allergens tested gave negative results
(12)	a dental nurse with persistent eczema of the hand had a positive patch test to glutaraldehyde and dental composite resin
(13)	2 hospital workers were exposed to glutaraldehyde while disinfecting endoscopes; both patients showed positive patch test reactions to a 1% aq. solution of glutaraldehyde and negative reactions to formaldehyde
(14)	a dental nurse was seen for a pruritic dermatitis that began on the hands and forearms and then spread to the upper arms and face; patch testing showed positive results to 1% thiuram, 5% nickel sulfate, 0.5% and 2% aq. glutaraldehyde, and 0.1% and 0.5% aq. benzalkonium chloride
(15)	the incidence of allergy to glutaraldehyde in HCWs was 33/266 (12.4%) for glutaraldehyde and 37/266 (13.9%) for formaldehyde; dual positivity to glutaraldehyde and formaldehyde was seen in 6 patients; nurses, physicians and dental assistants were most frequently affected
(16)	although glutaraldehyde was not included in the series of allergens tested, it was often added; in 1990, <1% showed positive patch test results; however, by 1994, that number had risen to >4%; more than 40% of sensitive patients were employed in the medical or janitorial industry

from 24 dermatology departments in Germany, the reported sensitization rate has climbed from <1% in 1990 to >4% in 1994 (16). Of these cases, more than 40% were employed in the medical or janitorial industries. In our study at the University of Kansas, 17.6% of HCWs tested to glutaraldehyde had a positive patch test suggesting allergic contact dermatitis. New cases of allergic contact dermatitis from glutaraldehyde among HCWs were noted as follows: 0 in 1994; 2 in 1995; 2 in 1996; 1 in 1997; 4 in 1998.

HCWs are chronically exposed to a variety of chemicals, sometimes unknowingly. In our study, the allergens that were considered statistically significant to HCWs all have an established link to the health-care industry. Glutaraldehyde, as mentioned earlier, has a wide variety of uses, but most commonly is used for sterilization. Thimerosal is used in the hepatitis vaccine, as an antiseptic, and as a preservative in topical preparations, especially ophthalmologic preparations. Thiuram mix is a commonly used accelerant in gloves. Benzalkoni-

um chloride is a sterilant. Methyl methacrylate is used in orthopedics and dentistry. Among the HCWs in our study that were sensitive to glutaraldehyde, nurses and dental hygienists/assistants were more likely to be allergic than were doctors and dentists. This probably indicates that exposure, and thus sensitization, to glutaraldehyde occurs among those cleaning the instruments rather than those using them. Furthermore, all subjects in our study (and most of those in the literature) suffered primarily from hand dermatitis, consistent with the exposure of workers responsible for cleaning equipment.

Allergic contact dermatitis has long been associated with atopy. However, in our study, sex, age, and history of atopy seem to have little bearing on allergic contact dermatitis to glutaraldehyde. This may indicate that glutaraldehyde is such a strong sensitizing agent that predisposing characteristics are often unimportant for sensitization to occur. Allergic contact dermatitis from glutaraldehyde has often been characterized as persistent. In fact,

Table 8. Outcomes of formaldehyde and glutaraldehyde patch testing

	Glutaraldehyde positive	Glutaraldehyde tested	Frequency (%)	Formaldehyde positive	Formaldehyde tested	Frequency (%)	Observed co-reactions	Expected co-reactions	<i>p</i> -value
HCWs	9	51	17.6	4	55	7.3	2	0.71	0.278
NHCWs	8	417	1.9	38	424	9.0	5	0.73	<0.001
Total	17	468	3.6	42	479	8.8	7	1.53	<0.001

many of the subjects of published case reports note the chronic nature of the disease leading some to change occupations. Such was our experience. Of those contacted for follow-up, 1/2 had completely changed jobs, while others had adjusted job requirements to control the dermatitis. Unfortunately, 1 patient who changed jobs still reports an occasional flare with only minimal airborne exposure. The 2 patients who continued to work in the same capacity continued to suffer from the allergic contact dermatitis.

The potential for allergen cross-sensitization between glutaraldehyde and formaldehyde has been hypothesized, despite an early study by Maibach (19) that downplayed such a link. However, in a 1989 paper, Fowler (2) referenced 2 studies (9, 11) that, when combined, yielded 5 out of 18 patients with dual sensitivities. Our study also supports the idea that co-reactivity between formaldehyde and glutaraldehyde may be multifactorial, including both a component of cross-reactivity and concomitant sensitization. Statistical evaluation of our data by χ^2 with Yates' correction (Table 8) yields an expected co-reactivity between glutaraldehyde and formaldehyde of 0.71 (*p*-value versus observed of 0.278), 0.73 (*p*-value versus observed of <0.001), and 1.53 (*p*-value versus observed of <0.001) for HCWs, NHCWs, and the total population, respectively. Thus, dual sensitivity to glutaraldehyde and formaldehyde in the total population occurred far more often than would be statistically expected. Co-reactions were also more frequent among HCWs, although the number tested was not large enough to give statistical significance. Since both allergens are contained in a variety of products and have similar chemical structures, it is difficult to determine if this co-reactivity is due to dual exposure or to immunologic cross-reactivity. However, if concomitant sensitization were occurring, we would expect to see a much higher proportion of formaldehyde allergy in HCWs when compared to NHCWs. Instead, the similar frequencies of formaldehyde allergy in both populations and the high frequency of glutaraldehyde allergy only in HCWs diminish the probability of concomitant sensitization. Nonetheless, since our sample is small, no generalizations can be made. More de-

tailed studies are needed to delineate the true cross-sensitizing relationship between formaldehyde and glutaraldehyde.

The treatment of glutaraldehyde-induced allergic contact dermatitis focuses on strict avoidance of the inciting allergen by the patient (20). Yet, convincing a patient with many years of training invested into his/her occupation to change jobs may be difficult. Instead, most patients attempt (usually unsuccessfully) to minimize exposure to glutaraldehyde. Currently, the National Institute for Occupational Safety and Health (NIOSH) recommends limiting glutaraldehyde exposure to no greater than 0.2 ppm (21). Polyethylene and spun-bonded polypropylene (e.g., Tyvek) coated with polyethylene, nitrile or butyl rubber gloves offer impervious protection from glutaraldehyde and should be used to minimize hand exposure (21). Additional eye, respiratory, and body protection is further recommended by NIOSH. However, the persistent nature of allergic glutaraldehyde dermatitis suggests that such recommendations and barrier protection are either not used or perform sub-optimally. The results of our limited study suggest that the former possibility may be more operative, at least in our population.

Stonehill et al. (22) described the use of glutaraldehyde as a sterilizing agent in 1963. Shortly thereafter, reports of its ability to cause allergic contact dermatitis became apparent. In the first published description by Sanderson & Cronin (5), the authors wrote, "Glutaraldehyde will be withdrawn from the theatre as soon as an alternative method of sterilization is installed." However, nearly 4 decades later, glutaraldehyde is still considered the sterilizing agent of choice in the cleaning of medical and dental equipment, despite published case reports and patch testing results that indicate its potential for sensitization and other toxic reactions. Its popularity seems to be driven by its cost, its disinfectant properties, its stability, and its lack of any significant damaging effects on equipment (23). Thus, despite awareness of glutaraldehyde's powerful potential to induce persistent allergic contact dermatitis, the rate of glutaraldehyde exposure and allergy appears to continue to rise, especially among those employed

in health-care professions. Until a less sensitizing disinfectant is developed, it requires those in health-care professions and other professions exposed to glutaraldehyde to heighten occupational safety standards and to improve methods of barrier protection.

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