Glutaraldehyde-induced and formaldehyde-induced allergic contact dermatitis among dental hygienists and assistants

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Glutaraldehyde is a simple, saturated, five-carbon dialdehyde with well-described sterilizing properties.[1] Its widespread use continues despite an extensive adverse effect profile, primarily because of its effectiveness as a rapid cold sterilizing solution and its relatively low cost.[2] Multiple studies[2-5] have confirmed the toxicities associated with prolonged exposure to glutaraldehyde, including the initial report of glutaraldehyde-induced allergic contact dermatitis, or ACD, by Sanderson and Cronin[3] in 1968.

It behooves those in professions exposed to glutaraldehyde to heighten occupational safety standards and to improve methods of barrier protection.

Shaffer and Belsito[2] reported an increased rate of glutaraldehyde-induced ACD among health care workers, or HCWs (17.6 percent), versus that among nonhealth care workers, or NHCWs (1.9 percent; $P < .001$), all of whom presented with signs and symptoms compatible with ACD. Researchers at the Nofer Institute in Lodz, Poland, similarly reported an enhanced incidence of glutaraldehyde-induced ACD among HCWs, as opposed to

ABSTRACT

Background. Research has found that among health care workers, dental personnel are especially likely to have reactions to glutaraldehyde and formaldehyde.

Methods. The authors conducted patch test evaluations with a voluntary cohort of randomly recruited, healthy dental hygienists, or DHs, and dental assistants, or DAs, and nondental professionals to determine the incidence of glutaraldehyde-induced and formaldehyde-induced allergic contact dermatitis, or ACD; the potential for coreactivity between glutaraldehyde and formaldehyde; and the correlation between training methods in safe handling of sterilizing solutions and the sensitivity to glutaraldehyde and formaldehyde among DHs and DAs.

Results. The researchers enrolled 101 DHs and DAs and 51 nondental professionals in the study. All except one DH/DA subject were female. The dental subjects' mean age was 34.3 ± standard deviation of 10.7 years; the nondental subjects', 33.8 ± 11.0 years. DHs and DAs had worked in their profession for a mean of 11.0 ± 9.3 years. Among the dental professionals, 80 (79.2 percent) had had a known exposure to cold sterilizing solutions, while the remainder were unable to provide a known history of exposure. Eleven (10.9 percent) dental professionals had clear reactions to glutaraldehyde, four (4.0 percent) were questionably allergic to glutaraldehyde, and two (2 percent) were definitively allergic to formaldehyde. One (2 percent) control subject had a reaction to glutaraldehyde, and one other (2 percent) had a reaction to formaldehyde.

Conclusions and Clinical Implications. The authors found a statistically significant disparity in the rates of glutaraldehyde sensitivity among healthy DHs and DAs versus healthy control subjects (10.9 percent versus 2 percent reactively; $P = .02$). They found no evidence of cross-reactivity between glutaraldehyde and formaldehyde. The preponderance of reactions among the DHs and DAs suggests that their present safety practices are largely ineffective in protecting against sensitization to glutaraldehyde in sterilizing solutions.

NHCWs, who had eczematous dermatitides.[4] Both studies identified strikingly disproportionate rates of glutaraldehyde sensitivity among dental hygienists, or DHs, and dental assistants, or DAs.[2,4] The large number of sensitized HCWs has been attributed to repeated exposures to glutaraldehyde. The specific association with DHs and DAs (as well as medical nurses) was conjectured to be the result of more intimate exposure to glutaraldehyde during the actual sterilization process.[2]

A second allergen tested along with glutaraldehyde in the Shaffer and Belsito study[2] was the chemically similar formaldehyde. The possibility of cross-reactivity between these two chemicals had been postulated, with the thought that sensitivity to one allergen somehow might engender immunological mimicry with consequent cross-sensitization.[2,5] The likelihood of such a correlation was de-emphasized in Maibach's earlier study,[6] the primary confounder regarding the hypothesis being the distinction between co-reactivity and incidental concomitant exposure. However, the potential for co-reactivity between glutaraldehyde and formaldehyde needs to be reconsidered given the findings of several reports, including that by Shaffer and Belsito,[2] which demonstrated a far larger-than-statistically-expected number of dual sensitivities within the diseased population (subjects with active dermatitis) studied. We deemed that a more detailed study to assess concomitant ACD to glutaraldehyde and formaldehyde in randomly recruited healthy people was necessary.

The incidence of delayed-type hypersensitivity to glutaraldehyde continues to rise, presumably because of inadequate employee training in effective barrier methods.

Long-term morbidity associated with glutaraldehyde-induced ACD has been reported, including worsening ACD (primarily hand dermatitis), the need for occupational change, and recalcitrant and persistent ACD even after career changes.[2,4,5] The incidence of delayed-type hypersensitivity to glutaraldehyde continues to rise, despite glutaraldehyde's well-described ability to sensitize, presumably because of inadequate employee training in effective barrier methods.[2,4] In one study,[2] most glutaraldehyde-allergic HCWs denied having any occupational safety training before exposure to the substance, despite well-defined National Institute for Occupational Safety and Health, or NIOSH, guidelines[7] regarding its handling.

One shortcoming of previous patch test studies was that they did not account for selection bias. In all of these studies, patients underwent patch testing after eruption of their dermatitis. Our study sought to find the true incidence of glutaraldehyde-induced ACD among dental personnel by randomly testing 100 DHs and DAs who had and did not have any history of dermatitis. We conducted simultaneous formaldehyde patch testing to aid in the understanding of the complex relationship between concomitant allergic reactions to formaldehyde and glutaraldehyde. Finally, by contrasting the occupational training of and barrier methods used by the sensitized and nonsensitized hygienists and nurses, we sought to identify the techniques that result in reduced sensitization to glutaraldehyde. Thus, the aims of this study were threefold:

- to determine the true incidence of ACD to glutaraldehyde among DHs and DAs by patch testing a cohort of randomly recruited, healthy DHs and DAs, with or without active (< 10 percent body surface area) or past dermatitis;
- to assess for co-reactivity, cross-reactivity or both between glutaraldehyde and formaldehyde by simultaneously patch testing DHs and DAs and control subjects to glutaraldehyde and formaldehyde;
- to determine the extent to which inadequate barrier protection and occupational training contribute to glutaraldehyde-induced ACD among DHs and DAs.

SUBJECTS, MATERIALS AND METHODS

We randomly recruited 101 healthy DH and DA volunteer test subjects from both university-based and private community practices in metropolitan Kansas City, Kan., and Kansas City, Mo. We recruited 51 healthy, age-matched and sex-matched volunteer control subjects from outside the dental profession. To be included, a potential subject had to meet the following criteria:

- be a normal, healthy male or female DH or DA aged 18 years or older or an age-matched and sex-matched healthy nondental worker;
- be willing to follow the study protocol;

- have the ability to give informed consent, complete a preliminary questionnaire under the guidance of the investigator(s), follow instructions and return to the clinic for study visits.

Specifically excluded from the study were members of the following groups:

- any woman who was pregnant, actively planning a pregnancy or nursing;
- any person who had, within two weeks before participation in the study, received phototherapy (ultraviolet B or psoralen plus ultraviolet A) or any systemic therapy (corticosteroid, immunosuppressive agent, cytostatics, pentoxifylline, leukotriene antagonists or other medication) known or suspected to have an effect on ACD (volunteers on a stable maintenance dose of inhaled steroids for asthma could participate);
- a person who, within two weeks before participation in the study, had treated the test sites with topical therapies (such as tar or topical corticosteroids) that are known or suspected to have an effect on ACD;
- a person who had any other significant dermatologic or general medical condition that could interfere with the study evaluations (such as active ACD, psoriasis or a fungal infection) affecting more than 10 percent of the body surface area;
- a person who had any significant medical condition(s) that could compromise immune responsiveness (lymphoma, AIDS, another immunodeficiency disorder or a history of malignant disease);
- a person who had received an investigational drug within eight weeks before the study or who intended to use other investigational drugs during the course of this study;
- a person with alcoholism, drug dependency, mental disorder or other factors that could limit his or her compliance with the study, could interfere with regular visits and/or, in the opinion of the investigator, would otherwise render the volunteer ineligible for the trial.

The protocol and consent form used in this study were approved by the institutional review board's human subjects committee at the University of Kansas Medical Center (Kansas City, Kan.).

After giving informed consent, eligible volunteers (N = 152) were enrolled after completing, with the investigator(s), a standardized questionnaire, which included information regarding age, race, sex, work history, glutaraldehyde/formaldehyde exposure history, glove use, occupational safety training and atopic status (defined as history of atopic eczema, allergic asthma and/or allergic rhinitis). We then initiated patch testing using Finn Chambers (Epitest Ltd. Oy, Tuusula, Finland) patch test devices adhered with Scanpor tape (Alpharma Norgesplaster, Vennesia, Norway) applied to the upper and outer portion of the arm in a standardized fashion. Test allergens included glutaraldehyde (0.2 percent, 0.5 percent and 1.0 percent in petrolatum) and formaldehyde (0.2 percent, 0.5 percent and 1.0 percent in water). We applied three concentrations of each allergen to facilitate the differentiation between truly allergic positive responses and low-grade irritation responses, which are known to occur after exposure to these allergens. We acquired the 1 percent concentrations of the allergens from Chemotechnique Diagnostics (Malmö, Sweden) and diluted it to the lower concentrations for patch testing all subjects.

After initial placement of allergens, all subjects were examined in an unblinded fashion at both 48 and 96 hours by at least one of the authors, all of whom were thoroughly trained in the interpretation of patch test reactions. We graded the reactions from 1 (allergic reaction) to 6 (no reaction) based on morphology as previously described.[2] Grades 1, 2 or 3 were considered allergic reactions. Grade 4 reactions were interpreted as "possible" or "equivocal" reactions. The only subjects we considered allergic to glutaraldehyde or formaldehyde were those who reacted with an intensity of 1, 2 or 3 to at least the highest concentration of the allergen and those whose reactions also followed a logical dose-dependent pattern.

We entered, retrieved and evaluated data using software for database management (Microsoft Access 97 and Microsoft Excel 97, both manufactured by Microsoft, Redmond, Wash.) and analysis (SPSS Version 9.0, SPSS, Chicago). We used χ^2 analysis with Yates correction for small expected values and one-sided P values to assess the null hypothesis that DHs and DAs were not more likely than age-matched and sex-matched control subjects to become sensitized to glutaraldehyde, formaldehyde or both. To assess the impact of atopy and occupational training in the development of glutaraldehyde-induced or formaldehyde-induced ACD or both, we performed a one-sided hierarchical log-linear analysis. For all tests, we deemed differences significant if $P < .05$.

RESULTS

The DH/DA test group and the control group were generally well-matched (Table 1). We enrolled 101 healthy DHs and DAs together with 51 healthy control subjects. There was one man among the study population, and no men among the control population. Age and atopic history were comparable between the two groups. The only difference between the two groups was an overrepresentation of nonwhite subjects among the control subjects ($P = .001$).

Table 2 presents the results of the volunteers' exposure history to glutaraldehyde and formaldehyde. As expected, most DHs and DAs (79.2 percent) knew they had been exposed to glutaraldehyde, while significantly fewer control subjects (2.0 percent) had such known exposure. Some test subjects were uncertain of their specific exposure history (6.9 percent of DHs and DAs). With respect to formaldehyde exposure history, the large number of subjects—particularly control subjects (96.2 percent)—who reported no exposure history likely is a function of underreporting and lack of awareness. The ubiquitous nature of formaldehyde and formaldehyde-releasing materials in society (such as cosmetics and textiles) greatly increases the likelihood that large numbers of both test subjects and control subjects had been exposed to formaldehyde at some time in the past.

TABLE 1

SUBJECT DEMOGRAPHICS.

SUBJECT GROUP	CHARACTERISTIC				
	Female (%)	Age (Years) ± SD*	Race (%)	History of Atopy† (%)	Work History (Years) ± SD
Dental hygienists/ dental assistants (n = 101)	99	34.3 ± 10.7	White: 90.1 African American: 6.9 Other: 3.0	28	11.0 ± 9.3
Control subjects (n = 51)	100	33.8 ± 11.0	White: 69.3 African American: 19.2 Other: 11.5	33	N/A‡

* SD: Standard deviation.
† Criteria: atopic dermatitis, allergic asthma or allergic rhinitis, or any combination of the three.
‡ N/A: Not applicable. Control subjects did not work in occupations that would expose them to glutaraldehyde or formaldehyde.

TABLE 2

EXPOSURE HISTORY TO GLUTARALDEHYDE AND FORMALDEHYDE.

SUBJECT GROUP	GLUTARALDEHYDE EXPOSURE (%)			FORMALDEHYDE EXPOSURE (%)		
	Yes	No	Uncertain	Yes	No	Uncertain
Dental hygienists/ dental assistants (n = 101)	79.2	13.9	6.9	64.4	25.7	9.9
Control subjects (n = 51)	2.0	98.0	0	3.8	96.2	0

TABLE 3

INCIDENCE OF GLUTARALDEHYDE-INDUCED AND FORMALDEHYDE-INDUCED ALLERGIC CONTACT DERMATITIS.

REACTION TO TEST SUBSTANCE	NO. (%) OF SUBJECT GROUP WITH REACTION		*P* VALUE
	Dental Hygienists/ Dental Assistants n = 101	Control Subjects n = 51	
Definitive reaction to glutaraldehyde	11 (10.9)	1 (2.0)	.02
Questionable reaction to glutaraldehyde	4 (4.0)	0 (0)	.01
Definitive reaction to formaldehyde	2 (2.0)	1 (2.0)	.44

Contrasting glutaraldehyde-induced ACD between DHs and DAs and control subjects yielded statistically significant differences in

TABLE 4

ATOPIC STATUS IN DENTAL HYGIENISTS AND DENTAL ASSISTANTS WITH AND WITHOUT SENSITIVITY TO GLUTARALDEHYDE.

SENSITIVITY TO GLUTARALDEHYDE	TYPE OF ATOPIC CONDITION (NO.)					TOTAL NO. (%)
	AD*	AA†	AR‡	AD + AA	AD + AR	
Positive: n = 11	0	1	4	0	0	5 (45.5)
Questionable: n = 4	0	0	2	0	0	2 (50)
Negative: n = 86	2	3	10	1	5	21 (24.4)

* AD: Atopic dermatitis.
† AA: Allergic asthma.
‡ AR: Allergic rhinitis.

TABLE 5

OCCUPATIONAL TRAINING AND GLOVE USAGE AMONG DENTAL HYGIENISTS AND DENTAL ASSISTANTS.

SUBJECTS' SENSITIVITY TO GLUTARALDEHYDE	TYPE OF GLOVES WORN (NO.)					TRAINING* STATUS (NO.)
	Nitrile	Latex	Vinyl	Other	Unknown	
Positive: n = 11	0	9	2	0	0	0
Negative: n = 86	4	65	5	5	7	22
Questionable: n = 4	0	4	0	0	0	1
TOTAL	**4**	**78**	**7**	**5**	**7**	**23**

* Training: Refers to training in the safe handling of solutions containing glutaraldehyde.

sensitivity: 11 of 101 (10.9 percent) DHs and DAs versus one of 51 (2.0 percent) control subjects, $P = .02$ (Table 3). Glutaraldehyde-questionable reactions, as previously described, were defined as macular erythema without induration or spreading; 4.0 percent of DHs and DAs had equivocal reactions, while we observed no such reactions among control subjects ($P = .01$). We found no difference in the rates of formaldehyde sensitivity between the two populations and we observed no evidence of cross-sensitization between formaldehyde and glutaraldehyde in either population.

Even when we considered the potential for confounding differences in training between atopic and nonatopic subjects, atopic status did not predispose DHs and DAs to develop glutaraldehyde-induced ACD ($P = .2$). We found increased rates of glutaraldehyde-induced ACD, although not to a statistically significant degree, among subjects who reported a history of allergic rhinitis (Table 4).

An active dermatitis affecting less than 10 percent of the body surface area was reported by six of 101 (5.9 percent) DHs and DAs. In two of these six (33.3 percent), we detected glutaraldehyde-induced ACD and considered it to be at least partially etiologic. We did not further analyze the etiology of the dermatitis in the remaining four subjects with active dermatitis.

All of the DH and DA subjects routinely wore gloves for patient contact and contact with sterilizing solutions (Table 5). Most wore the same type of glove for both endeavors. The types of gloves reportedly worn included latex (78 of 101), vinyl (seven of 101), nitrile (four of 101) and other (five of 101). Seven of 101 DHs and DAs were unable to recall the specific type of glove they used. All DHs and DAs found to have a glutaraldehyde-induced ACD had worn either latex (nine of 11) or vinyl (two of 11) gloves for contact with sterilizing solutions. None of the 11 DHs and DAs sensitized to glutaraldehyde had received training in the safe handling of solutions containing this disinfectant. All four of the DHs and DAs with questionable reactions to glutaraldehyde wore latex gloves when handling sterilizing solutions, and only one of four reported having received occupational training in the use of glutaraldehyde-containing disinfectants. We did not observe sensitivity to glutaraldehyde in any of the four subjects who reported using nitrile gloves. Overall, the use of nitrile gloves, training in the safe handling of glutaraldehyde-containing solutions or both measures significantly reduced the risk of developing glutaraldehyde-induced ACD ($P = .04$).

DISCUSSION

We observed a statistically significant increased rate of glutaraldehyde-induced ACD among randomly recruited, healthy DHs and DAs when comparing them with age-matched and sex-matched control subjects. However, DHs and DAs were no more likely than control subjects to be allergic to formaldehyde. The standardized odds ratio that subjects with no training in handling glutaraldehyde would develop ACD to this chemical was significant; the 95 percent confidence interval was 1.044 to 1.506.

TABLE 6

NATIONAL INSTITUTE FOR OCCUPATIONAL SAFETY AND HEALTH GUIDELINES FOR HANDLING GLUTARALDEHYDE.*

TYPE OF EXPOSURE	RECOMMENDATION
Airborne exposure	Safe level: < 0.2 parts per million; respiratory protection needed at ≥ 0.2 ppm
Topical exposure	Gloves†: spun-bonded polypropylene/polyethylene, nitrile rubber or butyl rubber
	Glasses: chemically resistant, safety
	Other: body protection (spun-bonded polypropylene/polyethylene) if contamination likely

* Based on information from the National Institute for Occupational Safety and Health.[7]
† Latex or vinyl gloves do not afford an appropriate barrier.

In a 1998 study by Kiec-Swierczynska and colleagues[4] of 280 HCWs at the Nofer Institute in Lodz, Poland, who had skin lesions, 12.4 percent were found to be allergic to glutaraldehyde. Glutaraldehyde sensitization was highest among nurses, physicians and dental assistants, with rates of 16.5 percent, 13.5 percent and 33.3 percent, respectively. Furthermore, the incidence of such sensitivity appeared to have risen at the Nofer Institute over time: only one case of glutaraldehyde sensitivity was seen before 1993, while an average of 11 cases per year became the norm five years later.[4] In collective data from 24 university dermatology departments in Germany, the reported sensitization rate to glutaraldehyde climbed from less than 1 percent in 1990 to more than 4 percent in 1994.[8] More than 40 percent of the people represented in these cases were employed in the medical or janitorial industries. In our prior study,[2] 17.6 percent of HCWs tested for glutaraldehyde sensitivity had a positive patch test suggesting ACD. We noted new cases of glutaraldehyde-induced ACD among HCWs as follows at our institution: zero in 1994, two in 1995, two in 1996, one in 1997 and four in 1998.

ACD has long been associated with atopy. However, in our study, a history of atopy seems to have little bearing on glutaradehyde-induced ACD. This may indicate that glutaraldehyde is such a strong sensitizing agent that predisposing characteristics, such as a chronic nonallergic hand dermatitis, are not as critical for the induction of sensitization to glutaraldehyde as they are for less sensitizing chemicals.

The potential for allergenic cross-sensitization between glutaraldehyde and formaldehyde has been hypothesized,[2,5] despite an early study by Maibach[6] that downplayed such a link. However, in a 1989 article, Fowler[5] referenced two studies[9,10] that, when combined, demonstrated that five of 18 glutaraldehyde-allergic people also had allergies to formaldehyde. Our prior study[2] of patients with allergic-appearing dermatitis also supported the idea of co-reactivity between formaldehyde and glutaraldehyde. However, in the current study of randomly recruited, healthy DHs and DAs and control subjects, we observed no such correlation. Nonetheless, since our sample is small, we can make no generalizations. More detailed studies are needed to specifically assess the potential cross-sensitizing relationship between formaldehyde and glutaraldehyde.

The treatment of glutaraldehyde-induced ACD focuses on the patient's strict avoidance of the inciting allergen.[11] Yet, it may be difficult to convince a patient with many years of training invested in his or her occupation of the need to change jobs. Instead, most patients attempt (usually unsuccessfully) to minimize their exposure to glutaraldehyde. Table 6 delineates current NIOSH recommendations for handling glutaraldehyde.[7] However, the results of our prior limited study[2] and those of our current study clearly indicate that training of DHs and DAs in handling of glutaraldehyde and the use of appropriate barrier protection is deficient.

Stonehill and colleagues[12] described the use of glutaraldehyde as a sterilizing agent in 1963. Shortly thereafter, reports of its ability to cause

ACD began appearing. In the first published description of this condition, Sanderson and Cronin[3] wrote, "Glutaraldehyde will be withdrawn from the theatre as soon as an alternative method of sterilization is installed." However, glutaraldehyde still is considered by many to be the agent of choice in the sterilization of medical and dental equipment, despite its potential for sensitization and other toxic reactions and despite the introduction of other alternative cold sterilizing agents (such as orthophthaldehyde [0.55 percent] and peracetic acid [35-40 percent]). Glutaraldehyde's popularity seems to be driven by its cost, its disinfectant properties, its stability and its lack of any significant damaging effects on equipment.[13]

CONCLUSION

Despite awareness of glutaraldehyde-induced ACD and published guidelines outlining methods for its safe use,[7,14] the rate of ACD to glutaraldehyde remains unacceptably high, especially among DHs and DAs and other HCWs. Among our study populations, DHs and DAs were eightfold more likely to be allergic to glutaraldehyde than were control subjects. We observed no coreactivity between glutaraldehyde and formaldehyde among healthy DHs and DAs or control subjects, in contrast to our earlier findings in a diseased population, all of whom presented with an allergic-appearing eczematous dermatitis.[2]

In contrasting DHs and DAs with and without glutaraldehyde-induced ACD, we found that an atopic diathesis had no impact. However, appropriate barrier protection (nitrile gloves) and training in the appropriate handling of glutaraldehyde significantly decreased the risk of acquiring glutaraldehyde-induced ACD ($P = .04$). Therefore, it behooves those in health care professions and other professions exposed to glutaraldehyde to heighten occupational safety standards and to improve methods of barrier protection. Among HCWs in contact with glutaraldehyde in disinfecting solutions, nitrile, butyl rubber or spun-bonded polypropylene/polyethylene gloves should offer an adequate barrier against routine exposures to glutaraldehyde. ■

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