Short communication

Glutaraldehyde: an occupational hazard in the hospital setting

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Background: We report a series of 24 health-care workers with respiratory symptoms suggestive of occupational asthma due to glutaraldehyde exposure.

Methods: The history of asthmatic symptoms was investigated with peak expiratory flow rate (PEFR) monitoring, and in eight of the subjects, the specific bronchial provocation test (SBPT) was applied as reference standard for diagnosis of occupational asthma. Levels of glutaraldehyde were monitored in the challenge chamber during the SBPT. Work environmental levels of glutaraldehyde were measured from air samples collected at least once during the PEFR monitoring of endoscopy and theatre nurses. Specific IgE antibodies to glutaraldehyde were measured with a series of glutaraldehyde modified proteins.

Results: In the eight workers who underwent SBPT, the diagnosis of occupational asthma was confirmed by a positive reaction (late and dual reaction in five and in three subjects, respectively). The mean level of glutaraldehyde observed during the challenge tests was 0.075 mg/m^3 (range 0.065–0.084 mg/m^3). In 13 out of the 16 remaining workers, the serial PEFR monitoring showed a work-related effect. In three workers, there was no physiological confirmation of occupational asthma. Levels of glutaraldehyde from the air samples collected in the workplace were as follows: personal short-term samples (mean 0.208 mg/m^3; median 0.14 mg/m^3; range 0.06–0.84 mg/m^3), personal long-term samples (mean 0.071 mg/m^3; median 0.07 mg/m^3; range 0.003–0.28 mg/m^3). Measurements of specific IgE antibodies to glutaraldehyde-modified proteins were positive in seven patients (29.1%) according to a cutoff value of 0.88% RAST binding. The presence of atopy to common environmental allergens and smoking was not associated with specific IgE positivity ($P>0.05$; Fisher's exact test).

Conclusions: Our report indicates the importance of glutaraldehyde as an occupational hazard among exposed health-care workers. Intervention in the workplace, training of personnel handling this chemical, and accurate health surveillance may reduce the risk of developing occupational asthma due to glutaraldehyde.

Glutaraldehyde is used in the hospital setting for cold sterilization of endoscopes and other medical instruments not autoclavable. It is a constituent of developing solutions in radiographic film processing, and it is also a fixative used in histochemistry and electron microscopy. Glutaraldehyde can cause occupational asthma (1), which sometimes is due to sensitization (2). Cases are reported mostly from endoscopy units, operating theatres, radiographic departments, and pathology laboratories, where levels of exposure were well below the accepted occupational exposure limits (1, 3, 4).

Glutaraldehyde vapour has a strong irritant effect on the respiratory tract, eyes, and skin. The maximum exposure limit (MEL) of 0.2 ppm or 0.7 mg/m^3 has been reconsidered, and a new MEL of 0.05 ppm or 0.175 mg/m^3 has been proposed.

In this study, we describe a series of health-care workers with a history of asthmatic symptoms related to glutaraldehyde exposure.

Material and methods

The subjects included in the study were 24 health-care workers (21 female; three male) (mean age 38.6 years; range 22–57 years) reported to the SHIELD surveillance scheme (5). Their occupations were as follows: endoscopy nurse (n=16), theatre nurse (n=5), radiographic darkroom technician (n=2), and pathology laboratory technician (n=1). They had respiratory symptoms (cough, chest tightness, and wheezing) related to glutaraldehyde exposure, which improved on days away from work. All of them presented a time interval between first exposure to glutaraldehyde and onset of respiratory symptoms suggestive of occupational asthma (mean 6.7 years; range 1–20 years). In 10 of them (41.6%), the onset of cough, chest tightness, and wheezing was preceded by nasal symptoms (stuffiness, rhinorrhea, and sneezing) related to glutaraldehyde exposure for a variable interval of time (mean 5.3 years; range 6 months–10 years). At the time of referral, seven workers were current smokers and four ex-smokers. Pre-existing asthma was present in three workers (12.5%).

Skin prick tests were performed with common environmental allergens, and atopy was defined by at least one positive skin prick test with a wheal diameter greater than 3 mm.

Nonspecific bronchial responsiveness to histamine (Yan method) and spirometry (Vitalograph, Buckingham, UK) were assessed at referral, when subjects were still exposed to glutaraldehyde at work.

An immunologic evaluation for specific IgE antibodies to glutaraldehyde was carried out with a series of glutaraldehyde-modified proteins (2). Blood samples were taken at referral, when subjects were still exposed to glutaraldehyde at work.

Serial peak expiratory flow rates (PEFR) were monitored in the studied population. Workers were asked to measure PEF every 2 h from waking to bedtime. They were instructed to use a Mini-Wright peak flow meter and record the best of three readings reproducible within 20 l/min. Minimum criteria for a good quality record were considered to be PEF measurements over at least two work and rest periods with at least five readings per day. After linearization of meter reading, records were plotted with the Oasys-2 analysis program (6).

Specific bronchial challenges were carried out in eight workers as inpatients after they signed the informed consent. As recommended in most guidelines, the baseline FEV_1 had to be greater than 70% of predicted value and/or greater than 2 l, without any other contraindications such as heart disease, uncontrolled hypertension, etc. Those taking anti-inflammatory medications were withdrawn before the challenge. Inhaled bronchodilators were withdrawn according to their duration of action. Subjects were challenged to 0.9% saline and 2% glutaraldehyde on separate days. The test was done by painting the solution onto a 2 m^2 piece of cardboard in a challenge chamber for 15 min. Histamine bronchial responsiveness was assessed the day before and the day after the SBPT. SBPT was considered positive if there was at least a 20% fall in FEV_1 compared to baseline values. In the case of the absence of airway calibre changes, significant increases in nonspecific bronchial hyperresponsiveness (NSBHR) would have indicated the need for additional exposures in the laboratory and/or in the workplace before excluding a diagnosis of occupational asthma (7).

Glutaraldehyde levels in air were measured in the challenge chamber during the SBPT. Moreover, at least once during the serial monitoring of PEFR, environmental

levels were measured in the disinfection rooms where the endoscopy and theatre nurses reported in this study had worked. Environmental samples were collected with the sampler worn by the operator in the ''breathing zone'' (personal samples), both during activities likely to produce peak levels of glutaraldehyde (short-term over 20 min) and during periods when exposure was intermittent (long-term over 34–120 min). The method of sampling and analysis had been used in a previous study (1).

Results

Atopy to common environmental allergens was present in nine workers (37.5%). Details of lung-function measurements, nonspecific bronchial responsiveness, and results of RAST for specific IgE to glutaraldehyde are shown in Table 1.

In seven subjects out of 24 (29.1%), specific IgE antibodies to glutaraldehyde were positive (Table 1) according to a cutoff value of 0.88% RAST binding (2). The possibility of false positivity was raised for two subjects (nos. 11 and 18) who had a total serum IgE level greater than 150 kU/l, which can cause nonspecific binding (2). Specific IgE antibodies were then assessed again 6–7 months after the two workers were removed from exposure. The RAST percent binding dropped from 2.62% to 0.31% in subject no. 11 and from 4.16% to 0.86% in subject no. 18, while the total serum IgE levels remained approximately stable (758 and 745 kU/l after 6 months in subject no. 11) or increased (526 and 650 kU/l after 7 months in subject no. 18), suggesting that the original values represented specific sensitization. The presence of atopy to common environmental allergens and smoking were not associated with specific IgE positivity ($P>0.05$; Fisher's exact test).

Serial PEFR monitoring showed a work-related effect (8, 9) in 16 (66.7%) workers, three of whom also underwent SBPT with one dual and two late reactions. Of the eight workers with PEF measurements equivocal for a work-related effect, five underwent SBPT with two dual and three late reactions. The results of SBPT are shown in Table 2.

The mean level of glutaraldehyde in the air during the challenge tests was 0.075 mg/m^3 (range: 0.065–0.084 mg/m^3).

Levels of glutaraldehyde from the air samples collected in the workplace at the time of PEFR monitoring are shown in Fig. 1. They were as follows: short-term samples (mean 0.208 mg/m^3; median 0.14 mg/m^3; range 0.06–0.84 mg/m^3); long-term samples (mean 0.071 mg/m^3; median 0.07 mg/m^3; range 0.003–0.28 mg/m^3). The concentration of glutaraldehyde was higher than 0.175 mg/m^3 in seven personal short-term samples and exceeded 0.7 mg/m^3 in two of them. The concentration of glutaraldehyde was below 0.175 mg/m^3 in all but one personal long-term sample.

Discussion

In our study, the diagnosis of occupational asthma was confirmed through SBPT in eight workers. Levels of glutaraldehyde observed during the challenge tests were below the new proposed MEL (0.175 mg/m^3). We did not challenge control unexposed asthmatic subjects, as non-

Table 1. Details of lung function, nonspecific bronchial responsiveness, and results of RAST for specific IgE to glutaraldehyde in 24 health-care workers with respiratory symptoms related to glutaraldehyde exposure at workplace

	FVC (%)	FEV_1 (%)	PD_{20} (μmol)	RAST % binding	IgE (kU/l)
1 C	92	87	>8	0.67	14
2	61	53	4	0.34	95
3 C	98	76	3.3	pos. 1.3	80
4 A	93	90	6.5	0.51	570
5	102	91	7	pos. 1.44	20
6 A-X	80	71	0.12	0.54	76
7 C	89	75	5.8	0.24	37
8	70	64	0.32	0.36	115
9 C	84	62	7	0.32	29
10 A	104	96	2.8	pos. 2.32	110
11 A	89	77	1.6	pos. 2.62*	758*
12	92	74	3.2	0.27	28
13 X	80	72	6.4	pos. 1.08	79
14 A-C	119	107	0.75	0.49	120
15 A	67	54	2.5	0.37	270
16	89	73	1.4	0.43	55
17	97	64	0.25	pos. 2.05	79
18 A	85	77	4.8	pos. 4.16**	526**
19 A-X	106	78	>8	0.47	175
20	91	83	>8	0.39	38
21 X	110	101	4.2	0.55	19
22 A	86	65	>8	0.27	73
23 C	81	80	0.5	0.31	22
24 C	59	50	0.75	0.28	89
	Mean: 88.5	Mean: 75.8	Mean: 3.96		

A: presence of atopy to common environmental allergens; C: current smoker; X: ex-smoker; FVC and FEV_1: values expressed as % predicted; pos.: positive; PD_{20}: histamine (Yan method).
* Specific IgE=0.31, total IgE=745 after 6 months of removal from exposure.
**Specific IgE=0.86, total IgE=650 after 7 months of removal from exposure.

Table 2. Results of specific bronchial provocation tests to glutaraldehyde (GA)

Patient no.	Pre-test FEV_1 (% predicted)	% fall from pre-test FEV_1	Pre-test PD_{20} (μmol)	Post-test PD_{20} (μmol)	Concentration of GA in air in challenge chamber (mg/m^3)
3	80	34 (LR)	4	0.85	0.07
5	95	15 (ER)–30 (LR)	>8	2.8	0.084
7	70	28 (LR)	7	2.5	0.065
12	92	12 (ER)–32 (LR)	4.5	0.75	0.068
16	75	38 (LR)	2.5	0.25	0.084
19	80	40 (LR)	>8	Not done	0.074
20	90	24 (ER)–42 (LR)	>8	0.44	0.078
22	78	36 (LR)	>8	Not done	0.081

* no. refers to Table 1; ER: early reaction; LR: late reaction; PD_{20}: histamine (Yan method).

specific bronchoconstriction due to an irritant effect could be excluded in view of the following considerations: the subjects were exposed to low concentrations below the MEL; all the reactions observed were late, although in three subjects they occurred as part of a dual response; in subjects with dual response, there was no relationship with prechallenge histamine responsiveness, which increased only after the challenge, presumably as a consequence of the late reaction.

In the remaining workers, the SBPT as reference standard for diagnosis of occupational asthma was not applied; however, the serial PEFR monitoring showed a work-related effect and confirmed the history of work-related respiratory symptoms in 13 of them. The measurement of glutaraldehyde levels in the workplace at the time of PEFR monitoring showed that only in some cases could exposures have reached an irritant threshold. Those measurements were not carried out throughout the period of the PEFR monitoring, but they were made at least once, probably reflecting the occupational exposure in the daily working activities. Some workers had inhaled steroids during the PEF record, but they were kept on the same dose to avoid masking work-related effects and real improvements on days away from work. In the original works of Burge et al. (10) and Burge (11), the use of antiasthma medication resulted in lower PEF sensitivity. In contrast, Malo et al. (12) showed that antiasthma medication did not affect the sensitivity and specificity of PEF readings, determined with specific bronchial challenges as reference standard.

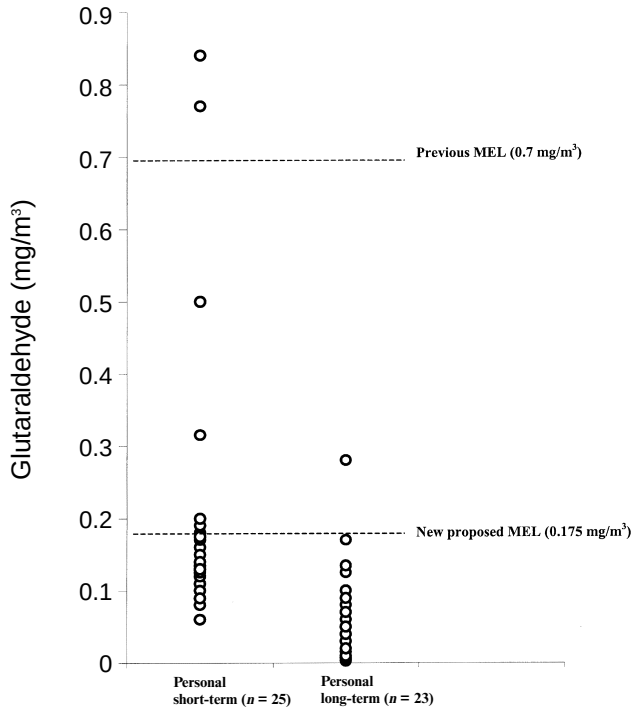

Figure 1. Levels of glutaraldehyde from air samples collected in workplace at time of PEFR monitoring.

Physiological confirmation of occupational asthma was not obtained in three workers (two radiographic darkroom technicians and one pathology laboratory technician).

Inflammation markers in the airways or in peripheral blood were not assessed together with specific IgE. In a previous study, Curran et al. (2) had detected a statistically significant difference for glutaraldehyde-specific IgE between exposed and unexposed subjects with total serum IgE less than 150 kU/l. The usefulness of determination of specific IgE to glutaraldehyde, as well as other low-molecular-weight chemicals, is certainly limited by the poor correlation with clinical symptoms. This may be due to the limitations of the current assay system, or other pathogenetic mechanisms may play a role in developing the condition. Venables et al. (13) showed that the length of time between the last occupational exposure and the date

the blood sample is taken reduces drastically specific IgE levels for low-molecular-weight agents and produces a negative result. However, in our study, cessation of exposure was not a complicating factor in the sensitivity of the assay, as workers were still exposed to glutaraldehyde in the workplace when the blood sample was taken.

In conclusion, our report indicates the importance of glutaraldehyde as an occupational hazard in the hospital setting. Use of extraction fans, respiratory protection, and training of personnel handling this chemical should be the first steps of any prevention strategy. The occurrence of respiratory symptoms in exposed workers should be promptly investigated to allow the early diagnosis of occupational asthma and removal from further exposure to avoid deterioration of the disease. Periodic health questionnaires, focused especially on the upper and lower respiratory tract, could be very useful to identify workers liable to develop occupational asthma due to glutaraldehyde.

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