

Occupational contact allergy to glyoxal

KRISTIINA AALTO-KORTE¹, ERJA A. MÄKELÄ^{1,2}, MARIA HUTTUNEN¹, KATRI SUURONEN¹ AND RIITTA JOLANKI¹

¹Section of Dermatology, and ²Department of Industrial Hygiene and Toxicology, Finnish Institute of Occupational Health, Helsinki, Finland

Glyoxal is a dialdehyde that is used as a disinfectant in health care and dentistry work. Allergic contact dermatitis from glyoxal has been described in these occupations. We analysed our patient data from 1998 to 2004 for allergic reactions to glyoxal. 20 patients had allergic reactions to glyoxal on patch testing. 5 of these patients worked in dentistry and 4 of them had present exposure to glyoxal. 9 patients were machinists without obvious exposure to glyoxal. A grinder with work-related facial dermatitis is described in detail. The chemical analysis of air samples from his workplace revealed 9.4–21 µg/m³ glyoxal. Glyoxal was also present in the used metal-working fluid, and apparently it had been formed during grinding. The remaining 6 patients worked in miscellaneous occupations and had no present exposure to glyoxal. Glyoxal is irritant on patch testing. Especially, solitary reactions to glyoxal 10% in aq. may be false-positive irritant reactions. 9 (45%) of our patients reacted to formaldehyde or glutaraldehyde. Glyoxal is an important allergen in dentistry and medical care, and we recommend it to be added to the antimicrobial patch test series. It also seems to be a 'hidden' allergen in the metal industry.

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Glyoxal (ethanedial, C₂H₂O₂, CAS 107-22-2) is a dialdehyde which is used in medical care and dentistry as a disinfectant for room surfaces, instruments and other equipment (1). Allergic contact dermatitis from glyoxal has been reported in a fibreglass worker from a polyvinyl resin emulsion (2) and from disinfectants in medical nurses (3–6), health care receptionists (3, 4), medical laboratory workers (3), dental nurses (1, 3) and hospital cleaners (6, 7).

Simultaneous allergic reactions to different aldehydes, formaldehyde, glutaraldehyde and glyoxal have been reported (1, 4, 6, 7), representing either cross-allergy or separate sensitization.

We analysed our patient data for patch test reactions to glyoxal at Finnish Institute of Occupational Health (FIOH).

Patients and Methods

Since November 1998, we have patch tested glyoxal in our antimicrobial series by the Finn Chamber[®] method according to the recommendations of ICDRG. The test preparations glyoxal 10% aq. and 1% aq. were diluted from synthesis grade chemical containing 40% glyoxal in water (Merck 820610). A commercial test substance,

glyoxal trimer (dihydrate, 1% pet.; Trolab, Hermall, Germany), has been tested since April 2000. In November 2003, 10% glyoxal was abandoned because it had caused many irritant reactions. All patients having a positive reaction to glyoxal interpreted as allergic (+, ++, +++) were analysed.

Results

Up until mid-year 2004, a total of 954 patients have been tested with glyoxal (266 with 1% and 10% glyoxal in aq., 614 with all of the 3 test preparations, 71 with 1% glyoxal in aq. and 1% glyoxal trimer in pet. and 3 with the trimer alone). The 10% concentration gave 91 (14.9%) irritant or doubtful reactions in 614 tests, with a reaction index of –0.78 (8). The reaction indexes for 1% glyoxal in aq. and 1% glyoxal trimer in pet. were –0.5 and 0, respectively.

20 patients (2.2%) had allergic reactions to glyoxal. The patch test results, some clinical and exposure details are shown in Table 1. Patient no. 1 has previously been described in detail elsewhere (1). One patient (no. 14) is presented as a case report below. The diagnosis of all the 20 patients was occupational allergic or irritant

Table 1. Clinical details, patch test results and exposure of patients with glyoxal allergy

Patient no.	Age (years)/sex	Occupation	Glyoxal					Formaldehyde	Exposure	Remarks
			10% aq.	1% aq.	Trimer 1% aq.	Glutaraldehyde	Formaldehyde			
Dental care										
1	44/female	Dental nurse	+	–	NT	++	–	–	4% glutaraldehyde and 4% glyoxal in a disinfectant	Ref. (1)
2	46/female	Dental nurse	++	–	++	+++	–	–	2.2% glutaraldehyde in a disinfectant	
3	52/female	Dental instrument cleaner	++	+	+	–	–	–	0.2% glyoxal in a disinfectant	
4	51/female	Oral hygienist	++	++	++	–	–	–	0.2% glyoxal in a disinfectant	
5	39/female	Dental nurse	NT	++	++	++	++	++	0.2% glyoxal in a disinfectant	Likely past exposure to glutaraldehyde and formaldehyde in disinfectants
Metal work										
6	48/male	Machinist	++	+	NT	–	–	–		
7	50/male	Machinist	++	+	NT	–	–	–		No glyoxal in chemical analysis of an MWF concentrate
8	36/male	Machinist	+	++	NT	–	++	++	0.54% formaldehyde in an MWF in chemical analysis	
9	45/male	Machinist	++	–	NT	–	–	–		
10	41/female	Grinder	++	?	++	–	–	–		
11	58/male	Turner	++	+	+	–	–	– (2% +)	0.11% formaldehyde in an MWF in chemical analysis	No glyoxal in chemical analysis of 3 MWF concentrates
12	27/male	CNC machinist	++	++	?	–	–	–		
13	40/male	Grinder	++	+	–	–	–	–		
14	58/male	Grinder	++	(2×) + (2×)	+	–	–	–	Glyoxal in the air and diluted, used MWF	No glyoxal in chemical analysis of an MWF concentrate also face dermatitis
Miscellaneous										
15	39/male	Medical researcher	++	++	NT	–	++	++	100% formaldehyde	
16	39/female	Textile shopkeeper, Ex public health nurse	++	+	NT	–	++	++	Formaldehyde in textiles (finishes)	Past exposure to glyoxal possible in health care
17	30/female	Hair dresser	++	–	?	–	+	+	Formaldehyde releasers in shampoos	
18	42/female	Gardener	+	–	–	–	++	++	Formaldehyde in a pesticide	
19	56/male	Truck driver and timber merchant	–	+	–	–	++	++	Formaldehyde in a shampoo	
20	28/female	Biochemist	++	–	–	–	–	–		False-positive due to 'angry back'?

NT = not tested; MWF = metal-working fluid.

contact hand dermatitis. 9 (45%) of the patients also reacted to formaldehyde or glutaraldehyde. The patterns of concomitant reactions are summarized in Table 1.

Case Report

Clinical symptoms and skin test results

Patient no. 14 was a 58-year-old grinder with a history of widespread folliculitis, but no atopy. He had worked in the metal industry since 1968. In the 1980s and 1990s, he had been working in floor casting with epoxy compounds for some time. In 1994, while employed as a grinder, he developed dermatitis on the back of his hands. In a local hospital in 1998, on patch testing with the standard series and oil and cutting fluid series, he had no allergic reactions. His dermatitis was compensated as an occupational irritant contact dermatitis caused by grinding fluids. He was able to continue his work by protecting his hands with nitrile rubber industrial gloves. In 2000, he developed an itching rash on his face. It appeared on workdays and always disappeared on longer vacations. At the workplace, the metal-working fluid (MWF) preparation was changed several times, but his skin symptoms did not improve.

The patient's folliculitis made the patch testing difficult to perform and interpret. At FIOH, 2 consecutive patch test sessions in September and November 2003 (the standard, antimicrobial, oil and cutting fluids, epoxy, plastics and glues, ethanolamines, isocyanates, metal, rubber, methacrylates and coco fatty acid derivatives series and the patient's own products) gave reactions to epoxy resins (epoxy resin ?+, brome DGEBA epoxy resin ?+, novolac epoxy resin +) and glyoxal (tested twice, results in Table 1). In May 2004, a dilution series in pet. prepared from the aforementioned synthesis grade glyoxal solution gave ++ reactions to 10%, 5% and 2.5% concentrations, a + reaction to 1%, and ?+ reactions to 0.5% and 0.25%. In the same session, glyoxal trimer (1% in pet.) gave a + reaction and 0.5% (diluted from the commercial test substance in pet.) a ?+ reaction.

In a challenge test at the workplace one Monday, the patient's face symptoms reappeared during the workday, and the following day severe dermatitis was seen on his face at FIOH.

Visit to the workplace

When enquiries from the manufacturers did not reveal any glyoxal or epoxy compounds in the products of the workplace, we decided to visit the patient's workplace one Friday in November

2003. We could not find any epoxy compounds or any other chemicals not reported by the patient. In a tidy workshop, there were 4 grinding machines of the same type, the grinding wheel in the centre. There were no enclosures or local exhaust ventilation for the machines. The machines were usually used one at a time for grinding small steel objects. At the time of our visit, the same MWF was in use in the machines, which the patient, at his clinical examination, had reported to use at work; it was also patch tested and was in use during the challenge test at the workplace. The spraying of the MWF into air was visible to the eye. The MWFs in the containers of the machines had a thick layer of metal dust-oil-foam on their surface. The workers and the workshop manager told us that separate chemicals to prevent bacterial growth in the MWFs were not used in the workshop, and neither could we find such preparations in the workshop.

We took air and liquid samples from the workplace for glyoxal analyses. A sample of non-diluted clean MWF was also taken into a plastic bottle. 2 air samples were collected by drawing air, 1.0 l/min, with portable SKC PCXR8 pumps (SKC, Eighty Four, PA, USA) through Sep-Pak[®] DNPH Xposure Cartridges (Waters, Milford, MA, USA) for 75 min. The sampling devices were placed on the machine in use: one at 0.5 m from the grinding wheel and the other near the worker at the end of the machine. 2 liquid samples of the diluted used fluid were taken from the MWF container of the machine by injecting 2 µl of the liquid directly into other DNPH Xposure cartridges while simultaneously drawing air through the cartridges. The direct injection to the cartridges at the workplace was carried out to prevent the possible glyoxal from degrading before the analysis. Glyoxal reacts rapidly with the 2,4-dinitrophenylhydrazine (DNPH) in the cartridges and forms a stable hydrazone derivative (9).

Chemical analyses

The MWF contained an additive mixture that was requested from the supplier as a separate sample. According to the product data sheet, it contained alkanolamines, carboxylic acids, polyglycols and polycarboxylic acids. The undiluted clean MWF and the additive mixture were injected to the DNPH Xposure cartridges in the laboratory in a manner similar to the procedure of taking the MWF samples from the grinding machine at the workplace.

The DNPH derivatives of glyoxal were extracted from the cartridges with acetonitrile

and analysed with HPLC/UV (9). Standard substances for the analyses were diluted from commercial glyoxal solution (40% solution in water, synthesis grade, Merck 820610). The air sample taken near the grinding wheel contained $21 \mu\text{g}/\text{m}^3$ of glyoxal and the air sample at the end of the machine near the worker contained $9.4 \mu\text{g}/\text{m}^3$. Glyoxal was evidently present in 2 fluid samples taken from the machine, but the amount was only about half of the limit of the quantification $0.2 \mu\text{g}/\mu\text{l}$. No glyoxal was found in the pure, non-diluted MWF or the additive mixture.

Formaldehyde analyses were not quantified from the workplace samples immediately, but afterwards the formaldehyde responses in the chromatograms were compared to the formaldehyde standard series that had been run earlier in similar analytical conditions. The air samples were approximated to contain considerable amounts of formaldehyde: $600 \mu\text{g}/\text{m}^3$ near the grinding wheel and $500 \mu\text{g}/\text{m}^3$ near the worker. The undiluted clean MWF contained about $2 \mu\text{g}/\mu\text{l}$ of free formaldehyde and the diluted dirty fluid samples about $0.5 \mu\text{g}/\mu\text{l}$.

The MWF and its additive mixture were also analysed for oxalic acid. It was determined as 1,2-diaminobenzene derivative with liquid chromatography and diode array detection (10). The complex matrix raised the limit of determination up to 10 mg/kg. The presence of oxalic acid could not be proven in either MWF or its additive mixture.

Discussion

Glyoxal is a difficult substance to patch test because irritant reactions occur. Especially a solitary reaction, resembling an allergic reaction to 10% concentration may be a false-positive reaction. The lower concentrations, 1% (in aq.) and trimer 1% (in pet.) are not so irritant and are able to reveal the relevant contact allergies almost as well (Table 1). A 10% concentration is too high, but some reactions may be missed with the lower concentrations. Now we plan to investigate 2% in aq.

Our patients belonged to 3 different groups (Table 1).

- (1) The first group consisted of 5 dental care workers, 4 of whom had present occupational exposure and obvious occupational allergic contact dermatitis from glyoxal. The glyoxal contact allergy of patient no. 2 was also considered occupational, representing either cross-allergy to glutaraldehyde or sensitization from past exposure.
- (2) The second group consisted of 9 machinists exposed to various MWFs, which usually

contain antimicrobials and might contain disinfectants such as glyoxal. Enquiries from the manufacturers did not reveal glyoxal, and chemical analyses of a total of 4 pure MWF concentrates (patients nos 7 and 11; Table 1) were also negative for glyoxal. In the case of patient no. 14, the 2 positive MWF samples were taken for the first time from the used fluid in the container of the machine. In this case, glyoxal was also found in the air samples from the workplace.

- (3) The third group consisted of 6 patients with different occupations and with no known exposure to glyoxal. Their glyoxal reactions were possibly false-positive reactions, or due to sensitization from previous exposure or cross-allergy to formaldehyde.

The positive glyoxal analysis of the air samples from the workplace of patient no. 14 was unexpected. No association between glyoxal and MWFs has been reported earlier. Our perusal revealed that no MWF or biocide meant for reducing microbial growth in MWFs had been declared to contain glyoxal in the Product Register of the Chemicals Register in 2003. The register contains data on more than 100 000 chemical products and is maintained by the National Product Control Agency for Welfare and Health in Finland. Enquiries to several MWF manufacturers in Finland and abroad did not reveal the use of glyoxal.

As glyoxal could not be found in the pure MWF concentrate, and no other chemicals were added to the fluid, we conclude that glyoxal was formed in the grinding machine. Glyoxal could originate (a) from heat-induced autoxidation of fatty acids, (b) from microbiological activity in the fluid (11), (c) from incomplete combustion of organic compounds (11–13) in the fluid during the grinding or (d) as a reduction product of the oxalic acid in the fluid.

Heat-induced autoxidation of fatty acids results in the formation of aldehydes, e.g. glyoxal. The process can be used in the production of glyoxal. For example, edible oils, such as sardine oil, may contain glyoxal up to 6.5 mg/kg (11). Aldehydes as the degradation products of fats are also a recognized hygienic problem in the food-processing and catering industries (14). Biodegradable synthetic oil and vegetable oil-based MWFs are likely to react similarly to edible oils and fats, as grinding generates the needed heat. The MWF used by patient no. 14 was a fully synthetic biodegradable fluid.

Metal-working fluids are well known for their high microbiological activity (option b) such as fermentation. According to the WHO report on glyoxal, it is a frequently detected compound in fermented food and beverages. The approximated amount we found, 0.1 µg/µl, is about 100-fold compared to the amount found in wine and 10 times less than that found in yogurt (11).

In the environment, automotive emissions and wood fires give rise to the formation of glyoxal due to incomplete combustion (11–13). The temperatures at the cutting edge can range from the ambient temperature up to 1000°C and thus option (c) cannot be ruled out.

We studied option (d). The additive of the MWF was declared to contain polycarboxylic acids, of which oxalic acid has the simplest molecular structure. Theoretically, oxalic acid can be reduced to glyoxal in alkaline, low-oxygen conditions in the presence of a metal catalyst. These conditions are possible in MWF containers under thick metal dust-oil-foam, when the fluid in the machine does not circulate and is not in touch with the air (especially during the week-end). In the chemical analyses, oxalic acid was not detected in the additive or in the MWF concentrate. However, the detection limit was quite high. Thus, we conclude that option (a) could be the most probable reason.

As an air impurity, glyoxal is not a common occupational problem, as glyoxal does not vapourize readily from aqueous solution. Therefore, occupational exposure by inhalation will probably take place only in conditions in which aerosols-containing glyoxal are released (11). Most countries, for instance Finland, have no threshold limit values for glyoxal in workplace air, but in the USA, the time-weighted average should not exceed 100 µg/m³ (TLV-TWA, 8 hr per day) (15). In Denmark, an air concentration of 500 µg/m³ must not be exceeded on any occasion at work places (16).

Metal-working fluids frequently contain additives that liberate formaldehyde. In our example case, the MWF contained 4,4-methylenebis-morpholine (CAS 5625-90-1), which is a formaldehyde liberator. The high air concentrations of formaldehyde (approximately 500 µg/m³) can be explained by the heat-induced degradation of the liberator in the grinding process. In Finland, the occupational threshold limit value is 370 µg/m³ for 8 hr exposure. In the USA, the level 0.3 ppm (approximately 370 µg/m³) should not be exceeded during any part of the working exposure (threshold limit value–ceiling, TLV-C) (15, 17).

The facial dermatitis of the patient was severe and suggestive of allergic contact dermatitis. We

could not find any other explanation for the rash and concluded that the patient had facial airborne allergic contact dermatitis due to glyoxal. As a part of a Finnish machinist study, air samples from 3 other metal workshops have been analysed, and small amounts of glyoxal (1.4–5.4 µg/m³) as well as other aldehydes were detected at 8 measurement sites (in about a half of those measured) near the worker's breathing zone. It is possible that the other machinists in this study were also occupationally sensitized to glyoxal. Thus, it might even be a relatively important 'hidden' allergen in the metal industry. In a previous report from Germany, in a group of 11 glyoxal allergic patients, there was a CNC turner with unclear exposure to glyoxal (7). We recommend that the determination of glyoxal should be arranged at workplaces for machinists with glyoxal contact allergy. The testing scheme should take into consideration that glyoxal may react rapidly with other compounds in samples taken from the workplace. Enclosures and local exhaust ventilation would reduce the exposure of the workers to aldehydes.

In this study, simultaneous reactions to several aldehydes were quite common, occurring in 45% of the cases. In the previous studies, the proportion has ranged from 14% to 64% (4, 6, 7). In the present study, glutaraldehyde allergy occurred only in dental workers. In this occupational group, most of the allergic reactions to the different aldehydes were in connection with obvious exposure, favouring the idea of separate sensitization. Cross-allergy to formaldehyde is a possible explanation for the glyoxal reactions, especially in the third patient group of miscellaneous occupations.

In conclusion, glyoxal is an important contact allergen in dental work and medical care, and we recommend that at least the commercial test substance, glyoxal trimer, should be added to the antimicrobial series or special series for these occupations. False-positive reactions to glyoxal 10% aq. are possible. We have observed many allergic reactions in machinists. Glyoxal was detected in the air samples and the used MWF from the workplace of a grinder with work-related facial dermatitis. Glyoxal seems to be a 'hidden' contact allergen in the metal industry.

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Address:

Kristiina Aalto-Korte
Section of Dermatology
Finnish Institute of Occupational Health
Topeliuksenkatu 41 a A
FI-00250 Helsinki
Finland
Tel: +358 30 4742292
Fax: +358 9 5875449
e-mail: kristiina.aalto-korte@ttl.fi