Occupational asthma due to glutaraldehyde and formaldehyde in endoscopy and x ray departments

P F G Gannon, P Bright, M Campbell, S P O'Hickey, P Sherwood Burge

Abstract

Background – Glutaraldehyde is the best disinfectant for fibroptic endoscopes. It is also used in the processing of x ray films. A number of studies have reported eye, nose, and respiratory symptoms in exposed workers. Three individual case reports of occupational asthma in endoscopy workers and a radiographer have also been published. We describe a further seven cases of occupational asthma due to glutaraldehyde in endoscopy and x ray departments, together with exposure levels measured during the challenge tests and in 19 endoscopy and x ray departments in the region.

Methods – Eight workers were referred for investigation of suspected occupational asthma following direct or indirect exposure to glutaraldehyde at work. They were investigated by serial measurements of peak expiratory flow (PEF) and specific bronchial provocation tests. Glutaraldehyde levels were measured using personal and static short and longer term air samples during the challenge tests and in 13 endoscopy units and six x ray darkrooms in the region where concern about glutaraldehyde exposure had been expressed. Three of the workers investigated with occupational asthma came from departments where glutaraldehyde air measurements had been made; the others came from other hospitals or departments.

Results – The diagnosis of occupational asthma was confirmed in seven workers, all of whom had PEF records suggestive of occupational asthma and positive specific bronchial challenge tests to glutaraldehyde. Bronchial provocation testing was negative in one worker who was no longer exposed and who had a less clearcut history of occupational asthma. Three workers also had a positive specific bronchial challenge to formaldehyde. The mean level of glutaraldehyde in air during the challenge tests was 0-068 mg/m³, about one tenth of the short term occupational exposure standard of 0-7 mg/m³. The levels obtained in the challenge chamber were similar to those measured in 13 endoscopy suites and six x ray darkrooms where median short term levels were 0-16 mg/m³ during decantation in endoscopy suites and <0-009 mg/m³ in darkrooms.

Conclusions – Glutaraldehyde can cause occupational asthma. The exposure levels measured in the workplace suggest that sensitisation may occur at levels below the current occupational exposure standard. (Thorax 1995;50:156–159)

Keywords: occupational asthma, glutaraldehyde, formaldehyde, hospital workers.

Glutaraldehyde (pentan-1,5-dial, glutaric dialdehyde) is an aliphatic dialdehyde with a slightly acidic and powerful odour perceptible at 0-16 mg/m³ which causes nasal and eye irritation at levels above 1-23 mg/m³. It is the best disinfectant for cold sterilisation of endoscopes, being active against bacteria, viruses and mycobacteria, and causes no damage to equipment. Glutaraldehyde is also a constituent of the developer used in x ray film processing, a fixative in electron microscopy, a biocide in cooling towers, a leather tanning agent, and a treatment for hyperhidrosis. In hospital endoscopy suites it has often been used in an open environment with uncontrolled exposure to workers. A number of studies have described eye irritation, rhinitis, and symptoms of airways obstruction at exposure levels below the 10 minute short term exposure standard of 0-7 mg/m³. There have also been several case reports of respiratory symptoms due to glutaraldehyde in endoscopy workers and one in a radiographer. These cases were diagnosed mainly by specific bronchial challenge. Glutaraldehyde is a recognised cause of occupational asthma for statutory compensation in the United Kingdom.

Despite these findings, there continues to be a degree of scepticism as to whether occupational asthma due to glutaraldehyde actually exists and, if so, whether it is due solely to an irritant effect. We have investigated a consecutive series of workers with direct or indirect exposure to glutaraldehyde referred to a specialist occupational lung disease clinic who were prepared to undergo occupational type bronchial provocation testing with glutaraldehyde exposure. We also performed controlled exposures to formaldehyde as several of the workers were also exposed to this chemical, and as occupational asthma due to formaldehyde is better described. We also report the exposure levels to glutaraldehyde from endoscopy and x ray departments in the region. These measurements were made at the request of the individual departments following concern about glutaraldehyde exposure. They are likely therefore to include more departments.
Occupational asthma due to glutaraldehyde

with above average exposures. Three of the workers investigated with confirmed occupational asthma came from departments where air measurements were made.

Methods
Subjects with exposure to glutaraldehyde and a history of asthmatic symptoms that improved when away from work were initially assessed by performing serial peak expiratory flow (PEF) measurements two hourly from waking to sleeping, at and away from work, over a four week period. These were then plotted\textsuperscript{13} and interpreted by eye for changes consistent with occupational asthma by an experienced observer. Specific bronchial provocation tests were performed on the subjects as inpatients. Subjects were challenged to 0.9% saline, 1% formaldehyde, and 2% glutaraldehyde on separate days. The test was done by painting the solution onto a two metre square piece of cardboard in a challenge chamber for 10 minutes. Forced expiratory volume in one second (FEV\(_1\)) was measured at regular intervals prior to and after the challenge. Methacholine or histamine challenges were performed on the day prior to and the day after the challenges using the Yan method. Occupational asthma was diagnosed when asthmatic symptoms occurred in relation to glutaraldehyde exposure and improved when away from exposure, and when the effect of exposure was also documented on serial two hourly PEF measurements. Occupational asthma due to glutaraldehyde was also diagnosed if exposure to low levels of glutaraldehyde during controlled specific bronchial challenge tests resulted in a 15% or more fall in FEV\(_1\), compared with values at a similar time following saline challenge.

To measure glutaraldehyde levels in air, a sampler was operated by the operator in the "breathing zone" (lapel) position to represent their actual exposure. Static samples were also collected by positioning the sampler at head height next to the bowls of glutaraldehyde. Short term personal and static samples were collected during the activities likely to produce peak levels of glutaraldehyde vapour ("worst case" work exposures) – for example, pouring used solution into a sluice or sink, activating and decanting fresh solution into disinfection tanks. Samples were collected over a period of 20 minutes or less, the sampling period being determined by the time required for the operator to complete the pertinent tasks, typically 10–15 minutes. Long term samples were collected over sampling periods ranging from 34 to 120 minutes during a theatre list when exposure was intermittent. During the list the operator usually assisted with the endoscopy procedure, returning to the disinfection area between patients to clean and disinfect the endoscopes. Static air samples were collected in x ray darkrooms over periods ranging from 25 to 140 minutes. Personal samples were also collected during simulated bronchial challenge when volunteers wearing respiratory protective equipment duplicated the standardised test procedures described above. Air samples were collected by drawing air at 1 l/min through glass fibre filters impregnated with 2,4-dinitrophenylhydrazine and phosphoric acid.\textsuperscript{14} The glutaraldehyde content of the filters was subsequently quantified by high performance liquid chromatography.

Results
Eight subjects were assessed for occupational asthma due to glutaraldehyde. Their details are given in table 1. Three were endoscopy nurses with direct and regular exposure to glutaraldehyde, one was a theatre nurse with similar but less regular exposure to glutaraldehyde mainly used for ENT instruments. One nurse worked on an ENT ward where laryngeal mirrors, auroscope, and static devices were sterilised in a very small covered trough in the sluice. Her asthma was lately provoked when in the ward and outside the sluice, although she used to sterilise the instruments herself. Three individuals were exposed in x ray departments. One was a darkroom technician with regular exposure to developers containing glutaraldehyde; one was a secretary who never entered the darkroom, but who reacted to newly developed x ray films when placed on her desk; one was a radiographer whose investigations excluded glutaraldehyde sensitisation. One worker had pre-existing asthma

| Diagnosis confirmed | Case 1 | F | 45 | Never | No | Yes | Endoscopy nurse | Glutaraldehyde | 7 years
| Case 2 | F | 53 | Never | No | No | Darkroom technician | Developer containing glutaraldehyde | 23 years
| Case 3 | F | 31 | Ex | Yes | No | Endoscopy nurse | Glutaraldehyde | 4 years
| Case 4 | F | 40 | Ex | No | Yes | x ray secretary | Developer containing glutaraldehyde | 6 months
| Case 5 | F | 29 | Never | No | No | ENT nurse | Glutaraldehyde | 4 years
| Case 6 | F | 25 | Ex | No | No | Theatre nurse | Glutaraldehyde | 2 years
| Case 7 | F | 42 | Never | No | No | Endoscopy nurse | Glutaraldehyde | 6 years
| Diagnosis not confirmed | Case 8 | M | 35 | Never | No | No | Radiographer | Developer containing glutaraldehyde | 10 years

Table 1 Details of eight patients with occupational asthma caused by glutaraldehyde

- Diagnosis confirmed
- Case 1
- Case 2
- Case 3
- Case 4
- Case 5
- Case 6
- Case 7
- Diagnosis not confirmed
- Case 8

- Occupation
- Agent(s) used at work
- Duration of exposure prior to onset of symptoms suggestive of occupational asthma

- Glutaraldehyde
- Developer containing glutaraldehyde
- 7 years
- 23 years
- Glutaraldehyde
- Developer containing glutaraldehyde
- 4 years
- x ray
- Developer containing glutaraldehyde
- 6 months
- ENT nurse
- Glutaraldehyde
- 4 years
- Theatre nurse
- Glutaraldehyde
- 2 years
- Endoscopy nurse
- Glutaraldehyde
- 6 years
- Radiographer
- Developer containing glutaraldehyde
- 10 years

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Table 2  Results of pulmonary function tests and bronchial provocation tests

<table>
<thead>
<tr>
<th>Patient</th>
<th>Diagnosis confirmed</th>
<th>Diagnosis not confirmed</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV₁ (% predicted)</td>
<td>% reversibility FEV₁ to 400 μg salbutamol</td>
<td>Serial PEF suggestive of occupational asthma</td>
</tr>
<tr>
<td>Case 1</td>
<td>106</td>
<td>0</td>
</tr>
<tr>
<td>Case 2</td>
<td>104</td>
<td>5</td>
</tr>
<tr>
<td>Case 3</td>
<td>77</td>
<td>13</td>
</tr>
<tr>
<td>Case 4</td>
<td>93</td>
<td>8</td>
</tr>
<tr>
<td>Case 5</td>
<td>82</td>
<td>0</td>
</tr>
<tr>
<td>Case 6</td>
<td>94</td>
<td>10</td>
</tr>
<tr>
<td>Case 7</td>
<td>102</td>
<td>7</td>
</tr>
</tbody>
</table>

FEV₁ = forced expiratory volume in one second; PEF = peak expiratory flow; PD₂₀ = provocative dose causing a 20% fall in FEV₁; M = methacholine; H = histamine; ER = early reaction; LR = late reaction (percentage fall from saline control shown in brackets, 15% or greater considered a positive reaction); SBPT = specific bronchial provocation test.

Table 3  Airborne levels of glutaraldehyde

<table>
<thead>
<tr>
<th>Concentration of glutaraldehyde in air</th>
<th>Median (mg/m³)</th>
<th>Range (mg/m³)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endoscopy unit personal short term samples (n = 11)</td>
<td>0-16</td>
<td>0-11-0-94</td>
</tr>
<tr>
<td>Endoscopy unit personal long term samples (n = 19)</td>
<td>0-041</td>
<td>0-003-0-28</td>
</tr>
<tr>
<td>Endoscopy unit static short term samples (n = 17)</td>
<td>0-17</td>
<td>0-006-0-84</td>
</tr>
<tr>
<td>Endoscopy unit static long term samples (n = 14)</td>
<td>0-016</td>
<td>0-005-0-52</td>
</tr>
<tr>
<td>x Ray darkroom samples (n = 19)</td>
<td>&lt;0-009</td>
<td></td>
</tr>
<tr>
<td>Simulated challenge samples (n = 3)</td>
<td>0-068</td>
<td></td>
</tr>
<tr>
<td>Occupational short term exposure standard (OES)</td>
<td>0-7</td>
<td>0-064-0-081</td>
</tr>
</tbody>
</table>

and three were ex-smokers; none were current smokers at the time of the investigation. Two were atopic in terms of positive skin prick tests to common environmental allergens. The period of symptomless exposure varied from six months to 23 years (median four years).

The results of the investigations performed are shown in table 2. Seven patients performed serial PEF measurements, all of which showed a pattern suggestive of occupational asthma. One patient had left his job as a radiographer at the time of investigation and so serial PEF measurement was not performed. All workers underwent specific bronchial challenge tests to the saline control and glutaraldehyde; one worker was not challenged to formaldehyde for technical reasons. Seven workers showed positive bronchial challenges to glutaraldehyde with falls in FEV₁ of 15% or more compared with the saline control. All showed late reactions although in two this occurred as part of a dual response. The results of breathing zone samples collected during three simulated specific bronchial challenge tests using 2% glutaraldehyde ranged from 0-064 mg/m³ to 0-081 mg/m³. Three out of four who had repeated measures of non-specific bronchial responsiveness showed increased responsiveness the day after the specific challenge to glutaraldehyde. Three workers also had positive late reactions on challenge to formaldehyde.

Thirty personal air samples were collected in 13 hospital endoscopy units. Twelve of these units employed manual methods of disinfection, simply immersing endoscopes in a bowl or trough of 2% glutaraldehyde solution; the remaining unit used an EW20 autodisinfector and, in this case, samples were collected whilst the disinfectant tank was drained to a bowl in front of the machine. The median value for personal short term samples was 0-16 mg/m³ (95% CI 0-12 to 0-68), for personal long term samples 0-041 mg/m³ (95% CI 0-016 to 0-14), and for static short term samples 0-17 mg/m³ (95% CI 0-12 to 0-25). In one department a personal short term level of 2-6 mg/m³ was measured when glutaraldehyde solution was poured over a semi-automatic trolley three times in a poorly ventilated room. As this is not recommended practice the results have not been included with the others which were measured when recommended procedures were being followed. A summary of the airborne levels is shown in table 3. Airborne concentrations of glutaraldehyde found in six x ray darkrooms were low, with all 19 samples collected being less than 0-009 mg/m³.

Discussion

Seven of the eight subjects investigated had occupational asthma confirmed by serial peak flow recordings and this was shown to be due to glutaraldehyde by specific bronchial challenge testing. The eighth subject had a negative bronchial challenge test and is unlikely to have occupational asthma due to glutaraldehyde. Three subjects had positive tests to formaldehyde suggesting crossreactivity between the two substances. Most of the reactions were late reactions, although two had an additional early reaction starting within 30 minutes after exposure. It is unlikely that the effect of glutaraldehyde on the airways was solely as an irritant as there was a latent interval after first exposure, the induced reactions were predominantly late rather than early, there was little relationship with baseline histamine responsiveness (four of the seven reactors had normal responsiveness before the challenge), and changes in

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responsiveness were seen following late reactions. Five of the seven cases of occupational asthma due to glutaraldehyde had no history of preceding asthma nor a history of rhinitis or eczema and were non-atopic on skin testing to common environmental allergens.

Glutaraldehyde is also a recognised skin sensitiser, indicating that it can induce a specific reaction in another organ. This contrasts with the effects on the eyes and throat when symptoms are common on first exposure and an irritant mechanism seems more likely.

Three of the affected workers came from departments where air measurements were made. The best method of exposure assessment is with short term samples which relate to the short term occupational exposure standard (OES). Longer term samples mask peak exposures but give an indication of bystander exposure. Beside the rather extreme example cited, only two measurements were above the short term OES. This suggests that sensitisation is likely to be occurring at levels below the current OES, particularly in x Ray departments where all air measurements of glutaraldehyde were low. Levels in the bronchial challenge chamber during the testing were well below the OES and lower than the 95% confidence intervals of the medians for the measured short term personal exposures.

The increased recognition of occupational asthma due to glutaraldehyde probably results from increased exposure. The practice of sterilising endoscopes has changed radically over the last 15 years, with much greater volumes of glutaraldehyde being used. x Ray developers also contain more glutaraldehyde than previously to compensate for the reduced silver content of the film.

This is the first series of workers to be described with occupational asthma due to glutaraldehyde and it confirms that glutaraldehyde asthma does exist. Its existence should be borne in mind when dealing with health care workers who complain of asthmatic symptoms that improve on days away from work. It indicates also that action should be taken to prevent further cases of occupational asthma arising. The best option would be to replace glutaraldehyde with a safer agent. There is scope to replace glutaraldehyde with steam sterilisation in most circumstances in the ward, clinic, and for dental use. However, other sterilising chemicals are generally less effective at endoscope sterilisation and may damage the instrument.15 It is also possible that the biological features that confer good sterilisation properties may be responsible for allergic properties and that other sterilising agents may also cause occupational asthma, rhinitis, and dermatitis. This is true of formaldehyde, chlorhexidine, isothiazolinones, and chloramine. In practice, therefore, glutaraldehyde should be replaced by steam sterilisation wherever possible. Where instruments are not autoclavable they should be processed in totally enclosed automatic washers, bearing in mind that specific steps should also be taken to protect the operator when refilling and draining disinfection tanks. Ventilation of these washers should be to the outside.

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