Asthma due to industrial use of chloramine

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Summary and conclusions

Seven brewery workers developed asthmatic symptoms after using chloramine (chloramine-T) powder as a sterilising agent. They gave positive weal and flare reactions to skin-prick tests with solutions of chloramine at strengths that caused no reactions in unexposed controls. The symptoms did not recur once the men had been removed from areas in which chloramine was handled.

As well as causing irritant effects, inhaling dry or liquid aerosols of chloramine may cause sensitisation, with workers being prone to allergic asthma on re-exposure. In view of this, measures should be taken to ensure that chloramine is not inhaled.

Introduction

While working as a medical officer to a brewery, one of us (MSB) found that some employees were developing nasal and chest symptoms, which appeared to occur when they handled the chlorine-liberating sterilising agent (Clortol; chloramine-T). Some of the men had developed severe asthmatic symptoms after routinely using the material, so further investigations were arranged in an attempt to elucidate the nature and cause of the symptoms.

Methods

We took health and occupational histories from seven brewery workers who had experienced symptoms after using Clortol to sterilise vessels and pipelines. Clinical examination was supplemented when possible by chest radiography, lung function tests, skin-prick tests,[1] blood counts, and serological measurements of immunoglobulins and precipitins. For the skin tests solutions of Clortol were made up in carbol saline; the other solutions were from Bencard. The skin-test results were recorded after 20 minutes. Precipitins were sought by Ouchterlony agar gel double diffusion tests.

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Results

Table I shows details of the seven men and their symptoms. None had a history of previous chest illness. One (case 7) had a history of eczema, hay fever, and allergy to penicillin. Two others had had non-respiratory allergic reactions, one to penicillin and the other to penicillin, tomatoes, and nylon. All but two had handled Clortol powder, tipping amounts of between 9 and 45 kg twice weekly into a container, then adding water to make up solutions of between 0·25% and 2% for sterilising purposes. Alternatively, they tipped the powder straight into water in a large vessel to be sterilised, and sometimes they sprayed the pre-mixed solution into the vessels. In all, about 50 tons (51 tonnes) of Clortol were used yearly.

One man (case 1) had experienced cough and nausea after exposure since first working with the material, but three years elapsed before he developed attacks of shortness of breath. In the other cases the latent periods between first being exposed to the powder and developing symptoms varied from a few days to two years. Once symptoms had been experienced, the latent periods between exposure and symptoms on subsequent occasions were short, none being longer than 10 minutes, and the symptoms lasted for between one hour and 30 days. Sometimes dyspnoea was severe, two of the men being sent to hospital and requiring intravenous aminophylline or corticosteroids. One man was given oxygen at work during his attacks, while others were treated with bronchodilators such as salbutamol or ephedrine. Two of the men found that initial respiratory symptoms of dyspnoea and wheeze would regress after an hour or so, only to return about eight hours later, awakening them in the night.

Four men experienced unproductive cough, although on one occasion one of them produced blood-flecked sputum after being heavily exposed. One man was prone to skin irritation and blistering after skin contact. Two of the men (cases 4 and 5), who had experienced a period of symptom-free exposure, developed symptoms for the first time immediately after an accidentally high exposure.

Table II shows serum IgE concentrations and blood eosinophil counts. Precipitins similar to those that developed when the patients' sera were tested against Clortol by simple agar diffusion could also be shown using fresh sera from controls not exposed to Clortol. Table III gives the results of skin-prick tests with common allergens and solutions of Clortol.

In all cases symptoms regressed and stopped when the men were removed from areas in which they were exposed to Clortol; the symptoms did not recur provided the men stayed well away from these areas.

TABLE I—*Details of seven men with symptoms associated with exposure to Clortol*

	Case No						
	1	2	3	4	5	6	7
Age (years)	43	55	56	37	49	29	43
Smoking (No of cigarettes daily)	30	10	30	15	30	–	–
Clortol handler	+	+	–	+	+	+	–
Other allergy	–	+	–	+	–	–	+
Latent period before first symptoms	1 year	2 years	2 months	1½ years	1 year	5 weeks	days
Duration of symptoms	2 days	2-21 days	1 hour	2-24 hours	2-14 days	1-30 days	3 weeks
Time spent off work or in hospital	–	Off work	Hospital	–	Off work, hospital	Off work	Off work
Symptoms:							
Lacrymation	–	+	–	+	–	–	–
Rhinorrhoea	–	+	+	+	–	+	–
Cough	+	+	–	+	+	–	–
Sputum	–	–	–	(+)	–	–	–
Dyspnoea	+	+	+	+	+	+	+
Chest pain	–	+	–	+	–	–	–
Skin irritation	+	–	–	–	–	–	–
Skin-prick test	+	+	+	+	+	+	+

TABLE II—*Serum IgE concentrations and blood eosinophil counts*

Case No	Interval between last exposure or symptoms and first tests	Interval between tests	Serum IgE (IU/ml)		Eosinophils ($\times 10^9$/l)	
			1st test	2nd test	1st test	2nd test
1	3 months	4 months	1450	600	0·800	0·094
2	3 months	1 year	500	100	0·512	0·066
3	2 years	9 months	2800	220	0·190	
4	2 months		3000		0·114	
5	10 months	2 years	3100	1000	0·412	0·312
6	2 months					
7	2 years		190		0·297	

Discussion

Chloramine-T (benzenesulphonamide, *N*-chloro-4-methyl-, sodium salt, molecular weight 281·7) is known by various names (appendix). It has been used during the past 60 years as a sterilising agent in the food and drink industries; to disinfect water; as a topical antiseptic for medical, dental, and veterinary purposes; and for various chemical tasks including detecting halogens. It is fairly soluble in water and practically insoluble in chloroform and ether. When ingested it is more toxic than the equivalent amount of chlorine as hypochlorite.[2] This is probably due to its reaction with amino-acids in the gastrointestinal tract to form toxic cyanogen compounds.[3]

Chloramine is described as an irritant and has been suggested to be a sensitiser,[4–6] but we can find no recent primary reference to its sensitising capacity, nor is this mentioned in other sources, such as Martindale's *Extra Pharmacopoeia*.[7] Nevertheless, except for the symptoms that occurred immediately after an accidental high exposure in cases 4 and 5, the histories in our cases were all more typical of allergic reactions than primary irritation. The noteworthy features, apart from the timing and nature of the illnesses themselves, were, firstly, the latent period between initial exposures to the material without ill effects and the time when similar or lesser exposures were followed by respiratory tract symptoms; and, secondly, that some men, working under the same conditions that had provoked symptoms in our patients, were unaffected. These features are consistent with findings in workers who had become sensitised to enzymes from *Bacillus subtilis* in the detergent industry.[8]

In all of our cases supporting evidence that immunological mechanisms played a part was supplied by the men's reactions to skin-prick tests (see table III). These unequivocal weal and flare "immediate" reactions (no late or delayed reactions occurred) were clearly not due to a primary irritant effect from the material itself or from liberated chlorine, as all but one of 25 controls, not occupationally exposed to chloramine, gave negative reactions. Nine of these controls were atopic. The only positive reaction in a control occurred in an extremely atopic woman to a solution of 10 mg/ml, the highest concentration of Clortol used. This reaction was not necessarily an artefact, as chloramine is incorporated in many cleansing agents and medicaments, one of which may well have sensitised her. If so, her exposure may have been much less than that experienced by our patients, for the brewery used some 50 tons of Clortol a year and four of our patients, two of whom were non-atopic, also gave positive reactions to more-dilute solutions. A feature of industrial sensitisation is that it is not necessarily confined to atopic people.[8 9] This may be due to the fairly large concentrations of airborne allergens compared with "natural" allergens such as grass pollens.

TABLE III—*Prick-test results**

Case No	Common allergens (Bencard)			Clortol concentration		
	Aspergillus fumigatus 10%	Group B_2 (pollens) grasses 2·5%	*Dermatophagoides pteronyssinus* 1·2%	10 mg/ml	1 mg/ml	0·1 mg/ml
1	0	0	3	10	5	—
2	—	0	0	13	6	5
3	—	0	6	10	8	4
4	—	0	0	4	itch	itch
5	0	0	0	5	5	—
6	—	0	0	4	0	0
7	—	4	3	5	0	—

*Weal reactions given as mean diameter (mm) at 20 min. 0 = Reaction not greater than control. — = Not tested.

Chloramine, with its relatively small molecular weight, could well be a hapten. Its reactivity, because of which it is used to radiolabel proteins,[10] could enable it to link with, or modify, amino-acid groups of proteins to form a molecule capable of bringing about an immunological response, with antibody formation. Whether or not the subsequent reaction on re-exposure is evoked directly by the unreacted material, as may happen with some other haptens,[11] the time lapse between such re-exposure and the ensuing reaction in the case of both inhalation exposure and prick test seemed no longer than would have occurred with antigens presumed complete.

The serum IgE concentrations were raised in both our atopic and non-atopic patients when measured fairly soon after illness occurring after Clortol exposure. In four of our patients, however, for whom two results were available, we found, as in the case of papain, another industrial allergen,[12] that this raised IgE concentration fell after a period free from illness and from exposure to the specific allergen. Similarly, we found in three patients that blood eosinophil counts fell after a period free from symptoms and exposure. The precipitins that developed when Clortol solutions were tested against the fresh sera of our patients by simple agar-gel diffusion tests could also be shown with the sera of controls not exposed to Clortol, but this does not necessarily preclude precipitin-mediated responses from having occurred. Nevertheless, the nature and timing of the illnesses and the results of the associated investigations indicated that the predominant reactions were type I, reagin-mediated ones.[13]

The acute chest symptoms experienced by our patients most probably derived from asthmatic airways obstruction, as indicated by the case histories and responses to bronchodilators and steroids. When they were no longer exposed to chloramine five of our patients appeared to recover completely from respiratory effects. Of the two others, one (case 2), although not complaining of symptoms, showed spirometric evidence of slight airways obstruction associated with auscultatory rhonchi when seen three months after being removed from an exposed area. As data obtained before exposure were lacking in this man, who had a history of smoking, we could not assume that Clortol had contributed to this defect; even if it had, a longer period of follow-up would have been necessary before we could have assumed that the change was permanent. The patient in case 5 had continued to be exposed to Clortol after its association with his symptoms had been established, and when seen three years after his first symptoms there was spirometric evidence of airways obstruction, reversible with isoprenaline, associated with an auscultatory wheeze. He too was a cigarette smoker. In both these patients details of lung function before exposure would have been helpful. Thus our patients had probably become sensitised to Clortol, and were prone to symptoms, including allergic asthma, on subsequent inhalation of dry or liquid aerosols of this substance. In the two men (cases 4 and 5) exposed to a heavy dose, even though their most immediate acute symptoms may have been due to direct primary irritant effects, the episodes appeared to ensure their sensitisation because they marked the end of a period of freedom from allergic symptoms on exposure to lesser amounts.

Since our investigation we have found that Feinberg and Watrous[14] obtained positive weal reactions to scratch tests with chloramine in 14 pharmaceutical workers with histories of asthma and rhinitis after its use. Although the scratch test is cruder than a prick test, causing greater and more variable trauma and dosage, these reactions were obtained at dilutions of chloramine up to and including 1:100 000 strength, while reactions were not elicited in controls, by scratch and endermal tests, with concentrations up to 1:1000 strength. Our prick-test

and other findings support their conclusions concerning the immunological importance of their results. We have also learned of two other men, at another brewery, each of whom developed severe dyspnoea requiring hospital treatment after handling Clortol. The men had been exposed to the material for one and 15 years before developing symptoms.

To prevent this sensitisation occurring we recommend that the following precautions be taken. Handling the material in dry, powder form in open conditions is inadvisable. Once sensitised, handlers and bystanders will not be able to work in the same part of the building as that in which chloramine is handled, since potentially severe asthma attacks may follow minimal exposure. Unless dispensed as a liquid and used in such a way that formation of aerosols is avoided, dry particles must be heavy enough not to become readily airborne. If the chloramine is in a fine powder form the containers should be airtight and opened only under water or in a glove box, or else with the operator fully protected, ideally by wearing an air-fed hood or suit or a properly fitting, appropriate filter-type mask, preferably pressurised. Laboratory workers should avoid spillages and open containers of the dry powder only in enclosed conditions or a fume cupboard. The principles of controlling health hazards from pulmonary sensitisers are similar to those recommended for enzyme powders.[15]

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APPENDIX—*Some preparations of chloramine (chloramine-T)*

Acti-chlore	Chloramin Heyden	Chlorosol	Heliogen
Aktiven	Chlorasan	Clorina	Kloramin
Anexol	Chloraseptine	Clorosan	Mannolite
Berkendyl	Chlorazan	Euclorina	Mianine
Chloralone	Chlorazene	Gansil	Tampules
Chloramine	Chlorazone	Gyneclorina	Tochlorine
Chloramin Dr Fahlberg	Chlorina Activin	Halamid	Tolamine

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Long-term parenteral exposure to mercury in patients with hypogammaglobulinaemia

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Summary and conclusions

Patients with hypogammaglobulinaemia commonly receive regular long-term replacement therapy with a concentrate of pooled normal human immunoglobulin G (IgG) containing an organic mercury compound (thiomersal) as a preservative. In 26 such patients the total estimated mercury dosage received ranged from 4 to 734 mg (mean 157 mg) over treatment periods of six months to 17 years (mean 6·5 years). Nineteen patients (73%) had raised urine mercury concentrations, but no correlation was found between urine mercury and the age of the patient, the IgG dose, or the duration of treatment.

Urine mercury concentrations are often used to control exposure and evaluate risks in exposed subjects. Hence most patients with hypogammaglobulinaemia are theoretically at risk from mercury exposure, although no clinical evidence of toxicity is yet apparent.

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Introduction

Hypogammaglobulinaemia is characterised by very low serum immunoglobulin concentrations resulting in recurrent infections with pyogenic organisms. The condition may be secondary either to protein loss from the renal or gastrointestinal tract or to depressed synthesis—for example, in reticuloendothelial malignancy—or it may arise as a primary condition of unknown aetiology. The usual treatment is regular administration of a concentrate of normal human immunoglobulin G (IgG) derived from pooled plasma (Blood Products Laboratory, National Blood Transfusion Service, Elstree, Herts) and containing about 150 mg IgG per ml: thiomersal (sodium ethylmercurithiosalicylate) is added at a concentration of 0·1 g/l as a preservative. Most patients are satisfactorily maintained on a weekly intramuscular dose of 25 or 50 mg/kg body weight,[1] and some patients have been given regular injections for over 20 years.

A potential long-term hazard of such treatment arises from the use of a mercurial compound as a preservative. In view of both the known toxicity of mercury and the relation between the duration of exposure and its effect on man we have examined the consequences of prolonged parenteral administration of a mercury compound in patients with hypogammaglobulinaemia.