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Atopic allergy to chloramine-T and the demonstration of specific IgE antibodies by the radioallergosorbent test

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Summary. Chloramine-T is a small molecular oxidizing agent that has been widely used as a disinfectant since the beginning of this century. It is generally used in a 5% solution but it is also supplied in powder form. Sporadic case reports of immediate-type sensitization to this agent associated with symptoms of asthma, rhinitis and urticaria have appeared during recent decades. In one of the reports, specific IgE antibodies in sera of four patients who developed asthmatic symptoms after exposure to chloramine-T were demonstrated using a radioimmuno-assay. Three cases of bronchial asthma in workers who had handled chloramine-T powder are described in the present report. Positive skin-prick test reactions to chloramine-T were observed and specific IgE antibodies to human serum albumin treated with chloramine-T were detected using the classic radioallergosorbent (RAST) technique in all three patients.

Key words: Chloramine-T – Radioallergosorbent test (RAST) – Occupational asthma

Introduction

Chloramine-T (N-chloro-4-toluenesulfonamide sodium salt) is a strong oxidizing compound with antiviral, bactericidal and fungicidal properties. It was introduced by Dakin et al. in 1916 [3] and was used extensively in World War I for the irrigation of infected wounds. Since then, it has been widely used as a disinfectant in hospitals, breweries and farms. There are different views as to the manner in which chloramine-T exerts its microbicidal action. Some authors claim that chlorine is the effective agent, whereas others believe the active component to be oxygen, or even both the former and the latter. Recent chemical evidence indicates that chloramine-T used in hydrolysis liberates hyperchlorous acid, which decomposes to chloride ions and oxygen, the latter being the disinfecting agent [3, 13]. Lately, chloramine-T has partly been replaced by other disinfectants, mainly due to the strong irritant effects of chloramine-T dust on the conjunctiva and mucous membranes of the respiratory tract. However, there are also a few reports on allergic reactions to this compound [1, 2, 4–8, 10, 14].

Within a 6-month period in 1985, three cases of occupational asthma were referred to the Department of Occupational Medicine. Those affected had been working at two factories in which they had packed different chemical products. Their work primarily consisted of packing disinfectants and cleaning products in liquid and powder forms. Chloramine-T powder was put into tins for 1- to 2-week periods, followed by 1- to 3-months intervals during which the workers were not exposed to the powder. Chloramine-T specific IgE antibodies were detected in sera of all three patients using the radioallergosorbent test (RAST).

Patients and methods

Case reports

Case 1. A 29-year-old, healthy, non-smoking woman with no familial or personal history of atopy had worked at a packing plant from 1974 to 1980 and then again from 1983 onwards. Since about 1974 she had noticed that she developed rhinoconjunctivitis while handling chloramine powder. During the winter of 1985 the symptoms became more pronounced, including facial erythema, nocturnal cough with dyspnoea and wheezing in the chest. The patient was diagnosed as having bronchitis by a general practitioner, but treatment with antibiotics had no effect. In March 1985 she was off-work for 2 weeks, during which the symptoms regressed and stopped. At 4 days after her return to work the symptoms recurred and she was referred to the industrial physician, who diagnosed bronchial asthma. Treatment with terbutaline was effective. A histamine provocation test did not reveal bronchial hyperreactivity. At this time the patient had not been exposed to chloramine-T for about 2 months. A skin-prick test using a standard panel resulted in a highly positive (3+) reaction to mugwort and a weakly positive reaction (1+) to Dermatophagoides pteronyssinus. However, the test results did not explain the patient's symptoms, which were closely related to exposure to chloramine-T. She was relocated to three different working areas at the plant; however, after a few days the airway symptoms returned at each site. The patient now

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works as a clerk for the same company and has experienced no further recurrence of her previous symptoms.

Case 2. A 33-year-old, healthy, non-smoking man with no familial or personal history of atopic disease had been working as an industrial mechanic since 1974; in 1984 he was stationed at the packing plant by which case 1 was employed. In January 1985, he was welding a container that was used for chloramine-T powder, he was exposed to dust but failed to notice any symptoms. In March 1985 the patient again repaired the same container, and after a few minutes he developed rhinitis. He thought he had caught a common cold and continued working until the following week. After completing this task, he went on sick leave and the symptoms disappeared after 1 day. During the spring of 1985, rhinits continually recurred within a few hours of days of his return to work, disappearing during weekends. The industrial physician was consulted and the patient was treated with nasal applications of sodium chromoglucate. However, the symptoms persisted during working hours. In August 1985, the patient was repairing an industrial vacuum cleaner containing chloramine-T when he experienced severe dyspnoea associated with wheezing in the chest. His symptoms were clearly work-related and he was referred to the Department of Occupational Medicine for consultation. The histamine provocation test revealed no symptoms of bronchial hyperreactivity. Skin-prick testing with extracts of birch, timothy, D pternoyssinus and cat yielded negative results. The patient returned twice to the plant, and symptoms of bronchial asthma recurred whenever he was exposed to chloramine-T. He now works as a hospital mechanic and exhibits no symptoms of airway allergy.

Case 3. A 46-year-old non-smoking woman with no personal or family history of allergy had been employed at another packing factory since February 1976. On a Friday in November of 1976, she experienced conjunctivitis and rhinitis as she was packing chloramine-T powder. The symptoms persisted over the weekend. Thereafter, the same symptoms recurred on weekdays and were accompanied by coughing and wheezing in the chest. In 1977 the patient was referred to the Department of Occupational Medicine for consultation because of her exposure to silica dust. On that occasion she did not associate her symptoms with exposure to chloramine-T, and her physician was not aware of the former exposure. She was treated with antibiotics, after which the symptoms disappeared. Between 1978 and 1982 the factory did not handle chloramine. In February 1982 the patient periodically developed bronchial asthma, and there was a clear-cut relationship to exposure to chloramine-T dust. In 1984 she was subjected to a skin-prick test using eight common airborne antigens; the results proved to be negative. As the patient kept a rabbit in her garden, and an allergen extract form rabbits was subsequently included in the test; this yielded a weakly positive (1+) reaction. However, this reaction could not explain her symptoms. A metacholine test showed no signs of non-specific bronchial hyperreactivity. For 2–3 months, the patient had been kept well away from areas in which she would have been exposed to chloramine-T.

In February 1985 an inhalation test was performed. The patient spent 5 min pouring a powder containing chloramine-T, which was used for disinfection of milk bottles, from one bowl to another. Bronchial obstruction, rhinitis and facial erythema developed and she experienced itching in her throat and dyspnoea; her peak expiratory flow (PEF) decreased from 340 to 220 l/min (35%) after 30 min. The obstruction was reversible: inhalation of terbutaline resulted in an increase in PEF to 300 l/min after 20 min.

In May 1985 another bronchial inhalation test was performed as described above using pure chloramine-T powder. After about 3 min the patient developed rhinoconjunctivitis and dyspnoea; her PEF fell from 370 to 155 l/min (58%) after 30 min. She developed an anaphylactic reaction associated with facial reddening and a decrease in blood pressure. Treatment comprising intravenous injections of corticosteroids and theofyllamine was given and the patient recovered completely within 3 h.

All three of the above patients were subjected to skin-prick tests using chloramine-T. Blood samples were also drawn and RAST tests for this compound were performed (see below).

Control group

A control group comprising ten atopic patients who had been sensitized to common inhalant allergens and ten nonatopics subjects were skin-prick-tested with chloramine-T solutions and RAST tests for chloramine-T were performed (see below). Atopic subjects were characterised as showing a skin-prick test reaction of $\geq 3+$ and/or a RAST class of ≥ 2 (> 0.7 PRU/ml) to at least one common airborne allergen.

Methods

RAST test. Commercially available paper discs with conjugated human serum albumin (Pharmacia Diagnostics AB, Uppsala) were incubated with 10 mg/ml chloramine-T (Merck, Darmstadt, FRG) in physiological saline for 2 h at room temperature. The solution was removed by suction and 50 mg/ml sodium metabisulfite in physiological saline was added. After incubation for 30 min at room temperature, the discs were washed twice in physiological saline and twice in phosphate buffer [0.05 *M* phosphate-buffered saline (pH 7.4) containing 0.2% bovine serum albumin, 0.1% Tween-20 and 0.02% sodium azide]. The discs tested negative ($<$ 0.35 PRU/ml) on RAST using non-atopic serum samples, showing IgE concentrations of 10–4,000 kU/l. Commercial chloramine-T discs (K 85; Pharmacia Diagnostics AB, Uppsala) were also used. RAST was performed according to the manufacturer's instructions (Pharmacia Diagnostics AB, Uppsala) using commercially available anti-IgE labelled with iodine 125 (Phadebas anti-IgE). The results were expressed in PRU/ml as derived from the Phadebas RAST Reference system (Pharmacia Diagnostica AB, Uppsala).

IgE determination. Serum IgE concentrations were determined by PRIST (Pharmacia Diagnostics AB, Uppsala). According to the manufacturer's instructions, the results were expressed in kU/l.

Skin-prick test. Chloramine-T dissolved in sterile distilled water at concentrations of 1 and 0.1 mg/ml was applied in skin-prick tests according to the Pepys methods [11] using a disposable blood lancet. Test reactions were scored in accordance with the Nordic guidelines [12], with wheal reaction to histamine (10 mg/ml) being graded as a 3+ reaction.

Results

All three cases showed skin-prick test reactions of $\geq 2+$ to chloramine-T. Specific IgE antibodies to human serum albumin treated with chloramine-T were detected. The results of skin-prick tests using various concentrations of chloramine-T and the measurements obtained for specif-

Table 1. Results of the skin-prick test and of RAST for chloramine-T and total IgE concentrations in 3 sensitized patients

Case	Skinprick test (number of pos. tests)		RAST (PRU/ml)	Total IgE (kU/l)	Other Sensitizations
	(0.1 mg/ml)	(1 mg/ml)			
1	2	3	0.5	50	Mugwort
2	2	2	2.5	55	None
3	2	2	2.9	320	None

ic and total IgE concentrations are summarized in Table 1. Both the skin-prick test and the RAST for chloramine-T were negative in the control groups.

Discussion

Allergy to chloramine-T was described in 1935 by Salén [14]. Since then, sporadic case reports have appeared in the medical literature [2, 6, 8]. The case histories and laboratory findings in the present study are in agreement with these previous reports. Kramps et al. [9] have demonstrated the occurrence of specific chloramine-T IgE antibodies in such cases using a solid-phase radioimmunoassay. In the present study specific IgE was measured by RAST. The test was easy to perform, gave representative results and enabled a semiquantitative expression of the results in PRU/ml according to the Phadebas RAST Reference System (Pharmacia Diagnostics AB, Uppsala). Exposure to chemical compounds that produce irritant effects on the conjunctiva and mucous membranes of the respiratory tract is not unusual in industrial occupations and is a common problem in occupational medicine. In individual cases it is not always easy for the physician to distinguish between symptoms of the common cold, bronchial hyperreactivity and atopic reactions to airborne antigens. This was well illustrated in the present study, in which all three workers had an allergy to chloramine-T but on occasion showed very non-specific symptoms. It is important that physicians be aware of the possibility of sensitization and that they relate to occurrence of symptoms to exposure.

Exactly how common such atopic sensitization to chloramine-T is in various occupational settings remains unknown. Apart from its use in industry, this substance is also used by farmers for sterilisation of milk bottles. We have recently become aware that additional workers at the above mentioned factories have developed allergy to chloramine-T. It is our view that allergy to chloramine-T may have been overlooked.

The risk of atopic sensitization is related to the time and dose of exposure. Occupational exposure to an allergen is often very high; therefore, sensitization and allergic diseases may also occur in individuals who are not predisposed to atopy. We described three cases whose exposure to chloramine-T was extensive. The duration of exposure in cases 1 and 3 was long. Case 2 was exposed for only a short time yet developed severe symptoms. This might be due either to a strong potential for sensitization to chloramine-T or to a very high level of exposure. The main pathway of sensitization probably involves the inhalation of dust or an aerosol. Chloramine-T is a strong oxidant and a low-molecular-weight compound. We believe that it reacts with many proteins to form complexes in which chloramine-T can be an antigenic determinant. The IgE antibodies are probably directed toward the chloramine-T haptenic part of proteins, since RAST functioned well with the complex of chloramine-T and human serum albumin coupled to the solid phase. Experiments performed by Kramps et al. [9] have shown that the paratoluene sulfonyl group probably is the antigenic determinant. Chloramine-T is a well known irritant and all three workers had been heavily exposed. However, none of the cases showed any sign of bronchial hyperreactivity in metacholine/histamine provocation tests. Allergy-induced bronchial hyperreactivity is known to decrease after the determination of exposure. Thus such an allergen-induced hyperreactivity in patients on sick leave who are awaiting examination by a specialist might be concealed. We conclude that there is strong evidence that although the immunological response observed in the present study was relatively weak, it indicates that the clinical asthma in all three cases was of allerginic origin.

Chloramine-T is a very useful antiseptic agent in dairy and other types of farming, in food-processing industries, in breweries and in medical care such as surgery and dental practice. However, there is a risk of sensitization and the benefit of its use should be weighed against the risks of adverse effects. An awareness of the possibility of airborne sensitization and careful handling instructions could reduce these hazards.

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