

CASE REPORT

Chlorhexidine—still an underestimated allergic hazard for health care professionals

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Abstract Chlorhexidine is a low molecular weight occupational sensitizer that can cause different delayed and immediate-type allergic reactions including anaphylaxis. It is widely used as an antiseptic and disinfectant and not only in the occupational environment as it is present in toothpaste, mouthwash, nose and eye drops and ointments. We present three cases of occupationally exposed workers with airway allergy to chlorhexidine. The role of chlorhexidine as an occupational allergen was confirmed by placebo-controlled specific inhalative challenge tests monitored by spirometry and analysis of induced sputum (influx of eosinophils after provocation has been observed). One of these patients presented with a systemic reaction with ordinary environment exposure. These findings are a reminder to clinicians of chlorhexidine's ability to cause various hypersensitivity reactions and the potential risk of this widely used antiseptic.

Key words Allergy; chlorhexidine; health care.

Introduction

Chlorhexidine (1,1-hexamethylene bis[5-(*p*-chlorophenyl) biguanide]) is a widely used antiseptic and disinfectant. It is a white or yellowish powder and soluble in water, ethanol and acetone. It retains its best biological activity and chemical stability in a solution with a pH of between 5 and 8. It has bacteriostatic and bacteriocidal effects on gram-positive and gram-negative bacteria and some mycobacteria, *Candida albicans*, and a virucidal effect on some viruses. It was first introduced in 1954 and has become one of the most widely used disinfectants in medical and non-medical environments. A wide variety of products contain digluconate and diacetate chlorhexidine salts, including creams, gels, wound dressings and other solutions that are used to disinfect the skin and mucous membranes, medical instruments and surfaces prior to different medical procedures. It is also a constituent of toothpaste, gargles, mouthwashes, nose and eye drops and ointments.

Chlorhexidine irritates the skin and mucous membranes (irritant contact dermatitis) and causes allergic reactions including delayed- or immediate-type hypersensitivity [1,2]. Contact sensitivity to

chlorhexidine was first reported by Calnan in 1962 [3]. Chlorhexidine can also cause contact urticaria, photosensitivity and occupational asthma. The first cases of anaphylactic reactions due to chlorhexidine were reported by Nomura in 1983 [4] and Nishioka *et al.* in 1984 [5]. Nishioka suspected an IgE antibody-mediated reaction. In 1986, Ohtoshi demonstrated specific IgE antibodies in the sera of eight patients with anaphylaxis due to chlorhexidine [6]. An increasing number of reports of anaphylactic reactions were published thereafter. In Japan between 1967 and 1989, 15 cases of anaphylactic shock due to chlorhexidine were reported (in 13 cases after application directly onto mucous membranes). Between 1965 and 1996, *The Committee on Safety of Medicines* in Great Britain collected 182 reports of reactions due to chlorhexidine-containing products [2]. The incidence of these reactions in occupationally exposed groups (especially health care workers) is not known. The prevalence of specific IgE antibodies to this compound among individuals with occupational allergy to chlorhexidine is also unknown.

We present three cases of health care workers admitted to the Department of Occupational Diseases, Nofer

Institute of Occupational Medicine in Lodz, Poland, on suspicion of having an allergic occupational disease.

Methods

In all patients, we performed a clinical examination, routine laboratory tests, chest X-ray (for differential diagnosis purpose), determinations of total serum IgE (Uni-CAP system Pharmacia Diagnostics, Uppsala, Sweden), specific serum IgE to chlorhexidine and natural rubber latex (Immunocap-100 System, Phadia, Uppsala, Sweden) and skin prick tests (SPTs) to common aeroallergens (dust mites, tree and grass pollens, moulds, feathers; Allergopharma, Germany) and to 0.01, 0.1 and 1% solutions of chlorhexidine. Resting spirometry and methacholine challenge test were also performed (Mijnhardt spirometer, The Netherlands). The patients were then subjected to a single-blind, placebo-controlled work-like condition specific challenge tests—the first with placebo (linen oil) and the second with 0.1% solutions of chlorhexidine. There was a 7-day break between the challenge tests. The subject painted the suspected substance onto a 1 m² wooden board by brush for 30 min. Cellular composition of induced sputum was analysed. Induced sputum samples were collected before the provocation and 4 h and 24 h afterwards. The processing of induced sputum and methacholine test methodology have been described elsewhere [7,8].

Case I

A 46-year-old woman had worked as a nurse for 23 years on the internal medicine ward. Chlorhexidine was a component of a variety of disinfectants that were used

there for different medical procedures. After 2 years of working as a nurse she developed recurrent non-productive cough and dyspnoea with wheezing (the first episode of dyspnoea took place while making beds in hospital rooms). She had never smoked.

The clinical and laboratory findings (including chest X-ray) did not reveal any abnormalities. Total serum IgE was within normal limits (38.6 kU/l). SPTs to common aeroallergens were negative. SPTs to 0.01% sol of chlorhexidine were positive (wheal of 5 mm). Specific serum IgE test for latex was negative. Specific serum IgE to chlorhexidine was positive (2.23 kU/l—class 2). On admission to hospital, resting spirometry revealed mild bronchoconstriction: forced expiratory volume (FEV₁) 2.66 l (72% predicted) and forced vital capacity (FVC) 2.87 l (70% predicted). Methacholine challenge revealed significant bronchial hyper-reactivity (PC₂₀ = 2.1 mg/ml). Challenge tests with linen oil (placebo) were normal. There were no changes in spirometry values, no clinical symptoms of bronchial obstruction and no significant changes in the induced sputum eosinophil count after exposure. On the day of specific challenge with chlorhexidine, resting spirometry was recorded: FEV₁ 2.64 l (71% predicted) and FVC 2.85 l (69% predicted). Ten minutes after chlorhexidine inhalation, the subject reported tightness in the chest, non-productive cough and dyspnoea. Wheezing was noted during medical examination and resting spirometry revealed a 21% drop in FEV₁ value. There was a slight drop in FEV₁ values between first and fourth hours and a significant drop in the fifth hour after the challenge (down to 32%; Figure 1). Methacholine challenge 24 h after chlorhexidine exposure revealed significant bronchial hyper-reactivity

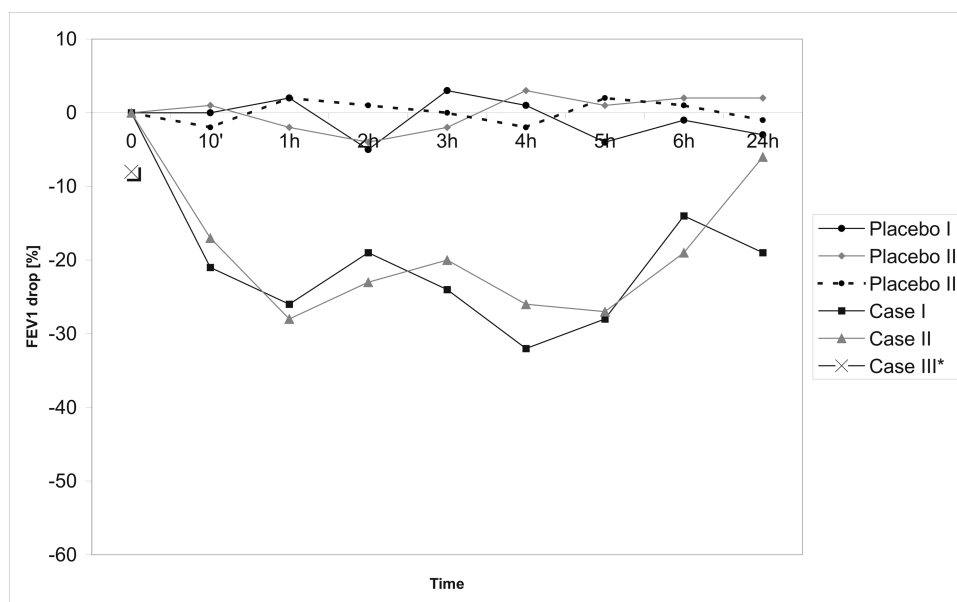


Figure 1. FEV₁ drop during placebo-controlled specific challenge tests with chlorhexidine. *Challenge test stopped due to anaphylactic reaction.

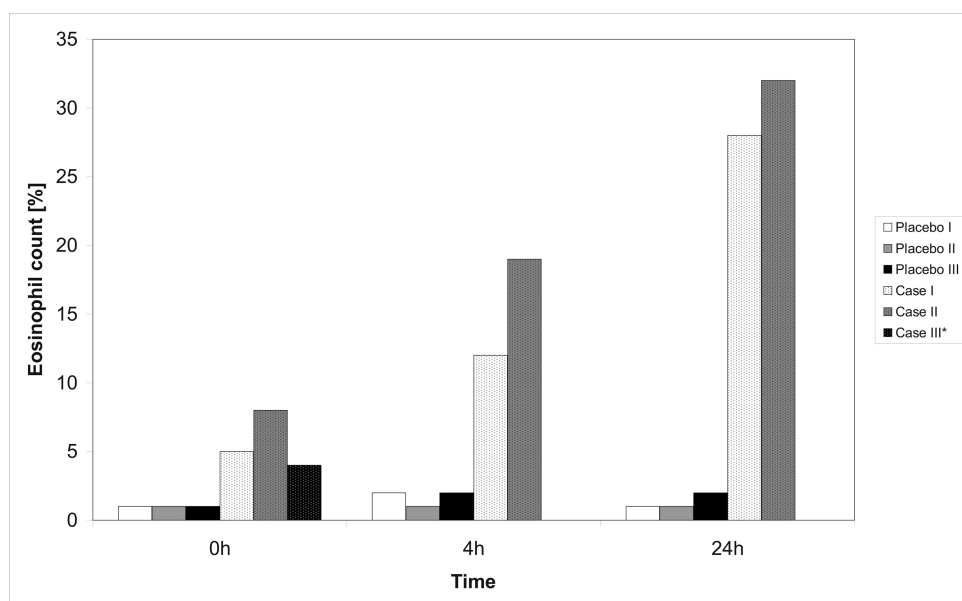


Figure 2. Eosinophil count during placebo-controlled specific challenge tests with chlorhexidine. *Not performed due to anaphylactic reaction treatment.

($PC_{20} = 1.1$ mg/ml). The eosinophil count increased in induced sputum (from 5% before to 12% 4 h and 28% 24 h after chlorhexidine exposure; Figure 2). Occupational asthma due to chlorhexidine was therefore diagnosed.

Case II

A 34-year-old woman had worked as a nurse for 10 years on a paediatric nephrology ward. Chlorhexidine was a component of various disinfectants that were used there for different medical procedures. After 8 years of working as a nurse, she developed recurrent non-productive cough, dyspnoea with wheezing, rhinorrhoea and paroxysmal sneezing. These symptoms appeared only while working in the hospital. She also reported several episodes of urticaria localized on the skin of her hands when she used latex gloves. She had never smoked.

Clinical and laboratory findings (including chest X-ray) revealed no abnormalities. Total serum IgE was within normal limits (30.9 kU/l). SPTs to common aeroallergens and chlorhexidine were negative. Specific serum IgE test for chlorhexidine was positive (1.17 kU/l—class 2). Specific serum IgE test with natural rubber latex was positive (5.59 kUA/l—class 3).

On admission to hospital, resting spirometry was within normal limits: FEV_1 3.70 l (119% predicted) and FVC from 4.07 l (114% predicted). Methacholine challenge test revealed significant bronchial hyper-reactivity ($PC_{20} = 1.6$ mg/ml).

The challenge test with linen oil (placebo) was normal. No changes in resting spirometry values, clinical symptoms of bronchial obstruction or significant changes in

eosinophil count in induced sputum after the exposure were observed.

On the day of specific challenge with chlorhexidine, resting spirometry was FEV_1 3.72 l (120% predicted) and FVC 4.42 l (124% predicted). Five minutes after chlorhexidine inhalation, the subject reported tightness in the chest, non-productive cough, dyspnoea, rhinorrhoea and sneezing. The wheezing was observed during medical examination and resting spirometry revealed a 17% drop in FEV_1 value. There was a slight drop in FEV_1 values between the first and the fourth hours and a significant drop in the fifth hour after the challenge (down to 28%; Figure 1). Methacholine challenge 24 h after chlorhexidine exposure revealed significant bronchial hyper-reactivity ($PC_{20} = 0.2$ mg/ml). An increased eosinophil count was observed in induced sputum (8% before, 19% in 4 h and 32% in 24 h after chlorhexidine exposure; Figure 2).

Specific challenge test with latex gloves was conducted 7 days after chlorhexidine challenge. At 6 min of latex gloves manipulation, the subject reported cough, dyspnoea, and worsening symptoms of rhinitis. Wheezing was observed during medical examination and resting spirometry revealed 22% drop in FEV_1 value. There was a slight drop in FEV_1 values between the first and the fourth hours and a significant drop at the fifth hour after the challenge (down to 25%). An increased eosinophil count was observed in induced sputum (10% before, 62% in 4 h and 63% in 24 h after latex exposure).

We also performed an exposure test with latex gloves that revealed urticaria on the dorsal hand surface after 15 min of donning the gloves. Occupational asthma and occupational allergic rhinitis due to chlorhexidine and natural rubber latex were diagnosed.

Case III

A 45-year-old woman had worked as a nurse for 24 years on the cardiology ward. After 22 years of work, she developed mild dyspnoea and urticaria, which appeared periodically during work, but she ignored her symptoms. Eventually she contacted her physician when she developed diffuse urticaria and dyspnoea during tooth brushing with chlorhexidine-containing toothpaste. She had never smoked.

The clinical and laboratory findings (including chest X-ray) were normal. Total serum IgE level was elevated (551 kU/l). SPTs to common aeroallergens gave positive result with *Dermatophagoides pteronyssinus*. SPTs to 0.01% sol of chlorhexidine were positive (wheal of 3 mm or above was considered as positive). Specific serum IgE test for latex was negative. Specific serum IgE test for chlorhexidine was positive (2.23 kU/l—class 2). On admission to hospital, resting spirometry was within normal limits: FEV₁ 2.68 l (115% predicted) and FVC from 2.87 l (105% predicted). Methacholine challenge did not reveal any bronchial hyper-reactivity.

Challenge tests with linen oil (placebo) were normal. No changes in resting spirometry values, clinical symptoms of bronchial obstruction or significant change in post exposure induced sputum eosinophil count were observed.

Five minutes after chlorhexidine exposure, she reported sore throat, hoarseness, throat tightness, mild dyspnoea and anxiety. Diffuse urticaria over the face and neckline was observed. The patient's blood pressure was slightly elevated (150/90 mm), and her heart rate was 120/min. The challenge was immediately stopped. Due to increasing symptoms of throat tightness, the patient was treated with 0.5 mg of subcutaneous epinephrine and 200 mg of intravenous hydrocortisone. Direct laryngoscopy revealed mild epiglottal oedema. The symptoms receded after 10 min. Methacholine challenge within 24 h after chlorhexidine exposure showed no bronchial hyper-reactivity. An occupationally related anaphylactic reaction to chlorhexidine was diagnosed.

Discussion

The described cases demonstrate how occupational allergy to chlorhexidine can take many clinical forms, be it skin, airway or even systemic manifestations.

Case I presents typical occupational asthma due to chlorhexidine that was confirmed by specific inhalation challenge test with significant changes in sputum eosinophil count after the exposure. Case II presents a situation where two occupational allergens may be responsible for a patient's symptoms. To our knowledge, this is the second known case of coexistence of latex and chlorhexidine allergy. Porter *et al.* described a case of anaphylactic shock in a pregnant woman during

gynaecological examination with latex gloves and an obstetric cream containing 1% of chlorhexidine [9].

Case III illustrates the symptoms of an occupational allergy becoming manifest due to exposure outside the workplace. The patient was occupationally exposed to chlorhexidine, but she ignored the mild dyspnoea and urticaria symptoms. When the symptoms appeared during tooth brushing with chlorhexidine-containing toothpaste, it prompted the patient to contact her doctor. Investigation revealed specific serum IgE to chlorhexidine and symptoms of diffuse urticaria and oedema of the larynx during inhalation exposure to this disinfectant. It is important to be aware that allergy to chlorhexidine (or other occupational allergens that can cause anaphylactic reactions) acquired in the workplace may induce reactions outside work (e.g. using chlorhexidine-containing toothpaste, mouthwashes, drops or ointments).

The identification of specific serum IgE in allergy testing to chlorhexidine is a reliable tool (high specificity and sensitivity) [10]. Inhalation challenge tests with assessment of clinical symptoms, spirometry changes and cellular changes in induced sputum or nasal lavage play a significant role in the diagnosis of chlorhexidine allergy (mainly for compensation for occupational disease).

Although occupational anaphylaxis is rare, it can be life-threatening and should prompt occupational health and safety services to improve health risk management (prevention).

Key points

- Chlorhexidine is an important occupational allergen used in medical and non-medical environments.
- The described cases demonstrate how occupational allergy to chlorhexidine can take many clinical forms, be it skin, airway or even systemic manifestations.
- The diagnosis was supported by clinical laboratory findings and specific challenge tests.

Conflicts of interest

None declared.

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Why I became an occupational physician...

Firstly I should explain why I became a doctor. My grandfather was science master at Hindley grammar school in Lancashire about the turn of the last century when with four children he re-entered Manchester University and studied medicine. He funded this course by teaching physics and chemistry at night class, which involved a 12 mile walk. After qualification he worked as an assistant in general practice before serving as medical officer in the trenches in France during World War 1. He had a great interest in shipping and on his half days took me from Bolton to Liverpool where we would travel on the overhead railway and view the merchant shipping in the docks and stately liners alongside the pier head.

My first house job was casualty officer in Liverpool where I established a working relationship with Dr J. Brown then medical superintendent of Cunard. I was enthralled and awestruck when he invited me to dine on board the liner *Sylvania*. Later, as a junior partner in a general practice, I was able to persuade his successor the irascible Robert Heggie, medical superintendent of the Cunard steamship company, to allow me to act as relief surgeon for a transatlantic voyage to New York in my holiday time. The experience exceeded all my expectations and was repeated annually in the early 1960s, during which time I acted as principal medical officer to various Cunard liners including RMS *Mauritania*, Queen Mary and Queen Elizabeth. On serving in RMS *Carinthia*, I transferred a moribund seaman with multiple injuries in an open boat in mid-Atlantic from a Norwegian freighter. I saved the man's life and the case received great publicity. Cunard remembered it when

they invited me at the age of 34 to be the fifth medical superintendent in the company's history, a position which I held for 30 years. Initially my remit included that of medical officer to Cunard Eagle International Airways but my most rewarding job with Cunard was to design and equip the hospital in QE2, and subsequently serve and work in my own hospital.

Thus I became an occupational physician and a founder member of the Faculty of Occupational Medicine. As the volume of shipping declined in the 1970s I was able to expand my interest in other industries and I have occupied diverse positions such as performing sessional work for the benefits agency on Merseyside, and establishing and running an occupational medical service for a large national consortium of private hospitals from their flagship hospital in the West End of London. I retired at the age of 76.

During a lifetime of occupational medicine I have been privileged to travel the world and meet and work with an incredible range of human beings, from the very highest and the bravest to the most disadvantaged. It has allowed me, amongst other things, to enjoy a high standard of living and indulge my taste in exotic motorcars, period houses, horticulture and travel.

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