

Chlorhexidine anaphylaxis: case report and review of the literature

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Chlorhexidine is a widely used antiseptic and disinfectant. Compared to its ubiquitous use in medical and non-medical environments, the sensitization rate seems to be low. Multivarious hypersensitivity reactions to the agent have been reported, including delayed hypersensitivity reactions such as contact dermatitis, fixed drug eruptions and photosensitivity reactions. An increasing number of immediate-type allergies such as contact urticaria, occupational asthma and anaphylactic shock have been reported. In the case report, we describe anaphylaxis due to topical skin application of chlorhexidine, confirmed by skin testing and sulfidoleukotriene stimulation test (CAST[®]: cellular antigen stimulation test). The potential risk of anaphylactic reactions due to the application of chlorhexidine is well known, especially that application to mucous membranes can cause anaphylactic reactions and was therefore discouraged. The use of chlorhexidine at a 0.05% concentration on wounds and intact skin was so far thought to be safe. Besides our patient, only one other case of severe anaphylactic reaction due to application of chlorhexidine on skin has been reported. Hypersensitivity to chlorhexidine is rare, but its potential to cause anaphylactic shock is probably underestimated. This review should remind all clinicians of an important potential risk of this widely used antiseptic.

Key words: allergy; anaphylaxis; chlorhexidine; drug allergy; hypersensitivity; cellular antigen stimulation test. © Blackwell Munksgaard, 2004.

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Chlorhexidine is a widely used antiseptic and disinfectant introduced in 1954. Compared to its ubiquitous use in medical and non-medical environments, the sensitization rate seems to be low. Multivarious hypersensitivity reactions to the agent have been reported, including delayed hypersensitivity reactions such as contact dermatitis, fixed drug eruptions and photosensitivity reactions. Knowledge of the possibility of sensitization is important regarding the increasing number of reported immediate-type allergies such as contact urticaria, occupational asthma and anaphylactic shock. In the following case report, we describe a well-documented anaphylaxis due to topical skin application of chlorhexidine.

Case Report

A 20-year-old woman presented for assessment of an anaphylactic event. The incident happened during a vacation on the beach. After an injury to the foot by a piece of broken glass, she disinfected the area with Merfen blue[®], a solution

containing chlorhexidine 0.05% and benzoxonium chloride 0.01%. Within a few minutes, she developed a generalized urticaria, angioedema, wheezing, dizziness, vomiting and diarrhoea, but no local reaction. She was taken to the nearest hospital where she was treated with systemic corticosteroids and calcium intravenously. She recovered completely and in good time.

She had no history of atopic diseases. Especially during wintertime, she complained of dryness of the hands. After a hot shower and fitness training, she frequently developed a pruritic rash on the upper part of her trunk and arms. In the past, she had had no allergies to medicaments though intestinal side effects from various antibiotics. Additionally, the ingestion of egg caused nausea and vomiting.

Allergologic Investigations

Prick tests with common inhalant allergens (*Alternaria tenuis*, *Cladosporium herbarum*, *Aspergillus fumigatus*, *Penicillium notatum*, *Ficus benjamina*,

Dermatophagoides pteronyssinus, *Dermatophagoides farinae*, dog, cat, grass, rye, birch, alder, hazel, ash, beech, mugwort, sorrel and latex) were negative. Prick tests with a large number of food allergens were also performed. There was a positive response to whole egg and egg albumin only.

We first tested chlorhexidine 1% in an open application only: dilutions of 1:10 000, 1:1000 and 1:100 were negative, but chlorhexidine 1% was strongly positive. Prick tests with chlorhexidine 1:10 000, 1:1000 and 1:100 were negative. Benzalkonium chloride 1:10 000, 1:1000 and 1:100, benzoxonium chloride 1:100, Merfen blue[®] were negative on prick testing and open application tests. All skin tests were read after 15–20 min.

In addition to skin testing, we also performed a lymphocyte stimulation test. No stimulation to chlorhexidine, benzalkonium chloride, penicillin G, amoxicillin or clindamycin was detected.

Specific immunoglobulin E (IgE) antibodies to SX1, latex, disinfectant mix, penicillin G, penicillin V, ampicillin and amoxicillin were also negative. Specific IgE antibodies to chlorhexidine were also determined (Laboratoire de Biochimie des Proteines et Centre de Tri, CHU Nancy, France). Specific IgE antibodies to chlorhexidine were negative [1.44%, $r = 1.42$ ($r < 2 = \text{negative}$)].

Blood analyses revealed normal concentrations for complement factors C3, C4, CH50, C1-esterase inhibitor and mast cell tryptase.

Finally, we performed a sulfidoleukotriene stimulation test (CAST[®], Bühlmann Laboratories, Schörenbuch, Switzerland) resulting in a high stimulation with chlorhexidine, but no stimulation with benzalkonium chloride. In this test, peripheral blood leucocytes are prestimulated with the cytokine interleukin-3 and exposed to the corresponding allergens. Mainly, basophils react by synthesizing sulfidoleukotrienes, namely LTC₄ and its metabolites LTD₄ and LTE₄. They are detected by enzyme-linked immunosorbent assay technique (1).

Discussion

Chlorhexidine is a synthetic cationic bis-biguanide antiseptic and disinfectant. Its white or yellowish powder is soluble in water, ethanol and acetone and retains the best biological activity and chemical stability in a solution with a pH of 5 and 8. It has eliminating effects on gram-positive bacteria and gram-negative bacteria, some mycobacteria, *Candida albicans* and some viruses. Introduced in 1954, it has become one of the most widely used disinfectants in medical and non-medical environments. As acetate or gluconate salt, chlor-

hexidine is used for topical application on skin or mucous membranes, wounds, burns, surgical instruments and surfaces. It is also found in toothpaste, gargles, mouthwashes, nose or eye drops and ointments. Moreover, the substance is used as a contraceptive, in lubricants, instillagels for urinary catheters and for impregnating central venous catheters.

Irritant contact dermatitis is a common adverse reaction to chlorhexidine. Apart from that, chlorhexidine is liable to a number of rare side effects (2), such as desquamative gingivitis, discolouration of teeth and tongue or dysgeusia (distorted taste). Contact with conjunctiva can cause permanent damage, and accidental contact with the tympanum can cause ototoxicity. There is one case published of bradycardia in a newborn caused by disinfection of the mother's nipple with chlorhexidine before breastfeeding.

Various allergic reactions due to chlorhexidine have been described. Contact sensitivity to chlorhexidine was first reported by Calnan in 1962 (3). Today, chlorhexidine is known to elicit allergic contact dermatitis (4–11, 19), including connubial contact dermatitis (12), generally after prolonged and repeated application. It can also cause contact urticaria (14, 37, 38), photosensitivity (5, 13), fixed drug eruption (15) and occupational asthma (16). People at particular risk of contact allergy are, apart from medical staff, patients with leg ulcers and leg eczema (17–20). Altogether, contact sensitivity to chlorhexidine seems to be rare (2). Some larger studies showed a sensitization rate of about 2% (6, 17, 21).

Even rarer are reports of immediate anaphylactic reactions due to chlorhexidine. The prevalence seems to be low, but exact data are missing. The first cases were published in 1983 by Nomura et al. (22) and in 1984 by Nishioka et al. (23). Nishioka et al. suspected a reaction mediated by IgE antibodies. In 1986, Ohtoshi (24) demonstrated IgE antibodies in the sera of 8 patients with anaphylaxis due to chlorhexidine. Today, there are an increasing number of reports of anaphylaxis due to chlorhexidine (25–51).

Analysis of these case reports suggests that patients with prior sensitization to chlorhexidine and with relatively mild contact dermatitis (10, 11, 40) have the potential for severe immediate-type reactions. Patients may have multiple episodes of anaphylaxis before the correct agent is identified (36, 40, 46). Chlorhexidine may cause anaphylaxis through the mucosal route at much lower concentration than elsewhere, generally as low as 0.05% (25–29, 32, 35, 39, 45, 49). Because of the number of anaphylactic episodes, the Japanese Ministry of Health recommended avoiding

the use of chlorhexidine on mucous membranes in 1984.

Some cases of severe anaphylactic reaction during anaesthesia associated with the use of chlorhexidine-impregnated central venous catheters were recently reported (31, 36, 43, 46, 47).

Application of chlorhexidine to intact skin can cause immediate allergic reactions such as urticaria, Quincke's oedema or dyspnoea and very rarely severe anaphylactic reactions (30, 33, 51). Evans (51) reported a mild anaphylactic reaction after application of chlorhexidine to a large burn wound, and Torricelli and Wüthrich (30) reported a severe anaphylactic reaction after application of chlorhexidine to minor scratches. Our patient developed a severe anaphylactic reaction after application of a solution containing chlorhexidine 0.05% to a small cut. To our knowledge, this is the second case report of such a kind, confirmed by positive skin tests and in addition confirmed by a positive sulfidoleukotriene stimulation test (CAST®).

Conclusion

The potential risk of anaphylactic reactions due to the application of chlorhexidine has been well known since the 1980s. Especially, its application to mucous membranes can cause severe anaphylactic reactions and therefore was discouraged. The use of chlorhexidine at a 0.05% concentration on wounds and intact skin was thought to be safe, because no severe anaphylactic reactions had been reported. Besides our patient, only one other case of severe anaphylactic reaction due to the application of chlorhexidine on skin is known. Hypersensitivity to chlorhexidine is rare, but its potential to cause anaphylactic shock is probably underestimated. This review should remind all clinicians of an important potential risk of this widely used antiseptic.

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