Chlorhexidine-induced anaphylaxis occurring in the workplace in a health-care worker: case report and review of the literature

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Parole chiave: Clorexidina; anafilassi occupazionale; operatore sanitario; disinfettante; sensibilizzanti

Summary

Background: Chlorhexidine has been widely used in the occupational field as an effective antiseptic and disinfectant, especially in the health-care services. Several cases of allergic reactions to chlorhexidine have been reported, both in the general population and in workers. Objectives: To describe a case of occupational chlorhexidine-induced severe anaphylaxis that occurred in the workplace in a health-care worker (HCW) and to update the literature on chlorhexidine as a possible occupational allergen. Methods: We report a case of a severe anaphylactic reaction that occurred in the workplace in a 63-year-old man, who had worked as a dentist for over 20 years. We also carried out a systematic review of the literature according to the PRISMA guidelines. No time or language filters were applied. Only occupational case-reports and case-series were included. Results: The causative role of chlorhexidine was suspected owing to the presence of chlorhexidine-containing products in the workplace. Positive results on the Basophil Activation Test confirmed the diagnosis of immediate chlorhexidine-induced hypersensitivity reaction and excluded a role of other disinfectants. No other causes of anaphylaxis were suspected. Our systematic literature review identified 14 cases of occupational chlorhexidine-induced allergy among HCWs; in these cases, the clinical presentation was mild and the symptoms resolved. No cases of systemic reactions in the workplace were reported. Conclusions: This is the first report of chlorhexidine-induced severe anaphylaxis occurring in the workplace. This case report underlines the importance of investigating and being aware of individual and environmental risk factors in the occupational field, which can cause, albeit infrequently, severe reactions with serious consequences.

Riassunto

«Anafilassi da clorexidina sul luogo di lavoro in un operatore sanitario: case report e revisione della letteratura».

Introduzione: La clorexidina è ampiamente utilizzata in ambito occupazionale come efficace prodotto antissettico e
Occupational Chlorhexidine-Induced Anaphylaxis

Introduction

Since its introduction in 1954, chlorhexidine, a synthetic bis-biguanide, has been widely used in the occupational field as an effective antiseptic and disinfectant, especially in the health-care services (e.g., peri-operative medicine and anesthesiology), for skin preparation, coating central venous lines and urinary catheters, and so on. Furthermore, chlorhexidine is one of the most commonly prescribed antimicrobial agents in the dental field (28), and can be found in a variety of therapeutics, including over-the-counter products (26). An increasing number of cases of delayed (type – IV, mediated by the cells of the immune system) and immediate (type I, IgE-mediated) hypersensitivity to chlorhexidine, including anaphylaxis, have been reported in the general population, particularly among surgical patients (e.g., in urology and gynecology). Chlorhexidine has been recognized as a cause of type – IV reactions such as allergic contact dermatitis, urticaria, photodermatitis and drug-related skin eruptions (5, 10, 12, 15, 17, 18, 20). Chlorhexidine IgE-mediated reactions can be very severe, with facial flushing, swelling and paresthesia, generalized urticaria or itching, difficulty in breathing and reduced blood pressure, and can require aggressive treatment with adrenaline. Rare anaphylactic reactions to chlorhexidine, first reported in 1984, are potentially life-threatening (20). The phenomenon

has been more frequently described in the occupational field, especially among Health-care Workers (HCWs), and may impair their occupational activity (1, 8, 14, 16).

Here, we report a case of occupational chlorhexidine-induced severe anaphylaxis that occurred in the workplace in a HCW. We also update the literature on chlorhexidine as a possible occupational allergen.

Methods

This case is reported in accordance with the CARE checklist (4).

Moreover, our systematic review of the literature was carried out in accordance with the Preferred Reporting Items for Systematic reviews and Meta-analyses (PRISMA) guidelines (11); we used a string of appropriate keywords, including “allergy”, “chlorhexidine” and “workers”, connected with ad hoc Boolean operators. Medical subject headings (MeSH) and wild-card options were utilized when appropriate. No time or language filters were applied. Only occupational case-reports and case-series were included. One study was excluded. All references cited in the studies included were searched in an iterative way, until no new study could be found. Target journals were extensively hand-searched. Further details of the search strategy used in the systematic review are shown in table 1.
For each study included, the following data were extracted: surname of first author, year of publication, country, age, gender, occupational activity of the patient(s), allergic history, type of exposure, clinical pictures, diagnosis, management/treatment and health outcome of the case.

RESULTS

This case of anaphylaxis involved a 63-year-old non-atopic man who had been employed as a dentist for over 20 years in outpatient dental clinics.

In August 2015, while at work, he experienced a systemic reaction characterized by the rapid onset of acute and diffuse urticaria and recurrent loss of consciousness; he was immediately treated with steroids and epinephrine in the workplace. At the Emergency Department, anaphylactic shock was suspected. More than one year earlier, he had referred two episodes of transitory loss of consciousness at work, without other typical characteristics of anaphylaxis; these episodes were attributed to laryngeal hyper-reactivity. Skin Prick Tests (SPTs) for common inhalant and latex allergens were negative.

Three months later the man was evaluated at the Allergy Unit of the San Martino Teaching Hospital in Genoa. Determination of Immuno-CAP (Thermo Fisher Scientific) for chlorhexidine-specific IgE
(sIgE) was prescribed. The result was 0.04 kU/L, together with a value of 46.7 kU/L of total IgE. A Basophil Activation Test (BAT) was also performed for all the products used in the workplace before the onset of anaphylaxis: indeed, the man’s working environment had previously been sanitized by means of an aerosol spray of various products containing phenol, ortho-phthalaldehyde and chlorhexidine. As the man had not worn any facial protection, he had been exposed via inhalation. BAT evaluates the expression of the activation marker CD63 on the membrane of basophils. The test is considered positive when CD63 on basophils incubated with the suspected agent is higher than 5.0% and when this expression is twice as high as that obtained with the wash buffer (stimulation index SI >2.0) (7). A clearly positive CD63 expression (14.5%) and SI=6.0 were recorded for chlorhexidine. This result was confirmed by testing a mouthwash containing chlorhexidine (CD63=9.6% and SI=4.0). All the other disinfectants tested proved negative (CD63 <5.0% and SI<2.0). The same disinfectant containing chlorhexidine proved negative in other sera, which were used as a negative control, as per usual laboratory procedures. The product that triggered the immediate systemic hypersensitivity reaction was a 2.0% solution chlorhexidine digluconate, mixed with other components (tetradecyltrimethylammonium bromide, dodecyltrimethylammonium bromide, isopropanol).

The systematic literature review retrieved and included 14 cases of chlorhexidine-induced allergy in HCWs. The characteristics of these cases are outlined in table 2. Exposure was mainly due to hand-washing with products containing chlorhexidine. In most cases, the clinical presentation was characterized by itching, redness and urticaria. Two cases of occupational asthma were also reported. Symptoms were generally mild and not persistent. The only anaphylactic reaction occurred in a nurse. In this case, some mild symptoms (i.e., urticaria and mild dyspnea) had occurred outside the workplace, dur-
Table 2 - General characteristics of 14 cases of occupational allergic reactions to chlorhexidine

| Reference                | Country | Age | Gender | Occupational activity | Allergic history | Type of exposure | Clinical picture                                      | Diagnosis                | Management/Treatment                           | Health outcome |
|--------------------------|---------|-----|--------|-----------------------|------------------|------------------|------------------------------------------------------|--------------------------|-----------------------------------------------|-----------------|
| Nagendran et al., 2009  | UK      | 31  | Female | Oncology-nurse        | No               | Chlorhexidine hand-washes | Itching and redness of wrists and forearms, urticaria | Clinical, sIgE          | 3 months after switching to non-chlorhexidine hand washes | Resolution of symptoms |
| Nagendran et al., 2009  | UK      | 51  | Female | Theatre-nurse         | No               | Chlorhexidine hand-washes | Itching and urticarial rash                           | Clinical sIgE           | Switching to non-chlorhexidine hand washes     | Resolution of symptoms |
| Nagendran et al., 2009  | UK      | 35  | Female | Endoscopy nurse       | No               | Powdered latex gloves + chlorhexidine hand-washes | Itching, redness of hands, rhinitis                    | Clinical, sIgE          | Avoiding wearing powdered latex gloves        | Persistence of symptoms |
| Nagendran et al., 2009  | UK      | 43  | Female | Domestic nurse        | No               | Chlorhexidine hand-washes | Hand dermatitis with secondary infection, urticaria of forearms | Clinical, sIgE          | Flucloxacillin and Dermovate, avoiding wearing powdered latex gloves | Resolution of symptoms |
| Toholka and Nixon, 2013  | Australia | 21  | Female | Graduate nurse        | No               | Chlorhexidine-based skin cleansers | Facial erythematous, pruritic eruption with localized edema | Clinical Patch tests    | Oral corticosteroids, avoiding chlorhexidine-based skin cleansers | Resolution of symptoms |
| Toholka and Nixon, 2013  | Australia | 20  | Female | Nursing student       | No               | Chlorhexidine-based hand rub   | Poplar eruption                                       | Clinical Patch tests    | Avoiding chlorhexidine-based hand rub and other products | Resolution of symptoms |
| Toholka and Nixon, 2013  | Australia | 21  | Female | Nursing student       | Yes (atopic eczema) | Chlorhexidine-based skin cleansers | Recurrent episodes of dermatitis                      | Clinical Patch tests    | Avoiding chlorhexidine-based other products  | Resolution of symptoms |
| Toholka and Nixon, 2013  | Australia | 28  | Female | Intensive care nurse  | No               | Chlorhexidine-based skin cleansers | Recurrent episodes of dermatitis                      | Clinical Patch tests    | Avoiding chlorhexidine-based products          | Resolution of symptoms |

(continued)
Table 2 (continued) - General characteristics of 14 cases of occupational allergic reactions to chlorhexidine

| Reference                | Country  | Age | Gender | Occupational activity                          | Allergic history | Type of exposure                                      | Clinical picture                                | Diagnosis                | Management/Treatment         | Health outcome |
|--------------------------|----------|-----|--------|-----------------------------------------------|------------------|-------------------------------------------------------|-----------------------------------------------|--------------------------|-----------------------------|------------------|
| Waclawaski et al., 1989  | UK       | 54  | Female | Nursing auxiliary                             | No               | Chlorhexidine aerosols                                 | Asthma                                        | Clinical Spirometry        | Not available               | Not available   |
| Waclawaski et al., 1989  | UK       | 43  | Female | Midwife                                       | No               | Chlorhexidine aerosols                                 | Asthma                                        | Clinical Spirometry        | Not available               | Not available   |
| Wittczak et al., 2013    | Poland   | 46  | Female | Nurse in the internal medicine ward           | No               | Use of chlorhexidine as disinfectant in different medical procedures | Non-productive cough and dyspnea with wheezing | Clinical SPT sIgE Specific challenge tests | Not available               | Not available   |
| Wittczak et al., 2013    | Poland   | 34  | Female | Nurse in the pediatric nephrology ward        | No               | Use of chlorhexidine as disinfectant in different medical procedures | Recurrent non-productive cough, dyspnea with wheezing, rhinorrhea and paroxysmal sneezing | Clinical, SPT sIgE Specific challenge tests | Not available               | Not available   |
| Wittczak et al., 2013    | Poland   | 45  | Female | Nurse in the cardiology ward                  | No               | Tooth brushing with chlorhexidine-containing toothpaste | Dyspnea and urticaria                         | Clinical, SPT sIgE Specific challenge tests (stopped due to anaphylactic reaction) | Not available               | Not available   |
| Vu et al., 2017          | Australia| 49  | Female | Endoscopy technician                           | Yes (contact dermatitis, allergy to aspirin) | Chlorhexidine-based hand rub                     | Urticaria on the hands and arms, chest tightness, dyspnea | Clinical, SPT, Patch tests | Avoiding chlorhexidine-based products | Resolution of symptoms |

sIgE: Specific IgE; SPT: Skin Prick Test
ing tooth brushing with chlorhexidine-containing toothpaste, and the anaphylactic reaction arose subsequently, during a specific inhalation challenge test with chlorhexidine (31).

**DISCUSSION**

To the best of our knowledge, this is the first report of occupational chlorhexidine-induced severe anaphylaxis occurring in the workplace.

Our results show that chlorhexidine, a well-known allergen in non-professional settings (19), should be considered a possible occupational allergen able to cause, albeit infrequently, severe reactions with serious consequences (13, 24).

Allergic sensitization to antiseptics/disinfectants containing chlorhexidine could be frequent and is likely to increase given the widespread utilization of these products in health-care settings, and hence the chronic exposure of workers. In our case, the sanitation procedures carried out in the dental clinics included daily cleaning and disinfection of environmental surfaces with aerosol products containing antiseptic/disinfectant.

The first two cases of asthma, which were confirmed by means of occupational challenge, were reported in 1989 by Waclawaski et al. (30), and revealed the risk of using chlorhexidine aerosol in health-care settings.

In 2003 a Danish cross-sectional study failed to ascertain any laboratory-confirmed allergy to chlorhexidine among 104 HCWs recruited (physicians, nurses, auxiliary staff); the authors concluded that IgE sensitization was a very rare event in the occupational field, despite considerable exposure (6).

In 2009, Nagendran et al. identified the first confirmed occupational IgE-mediated chlorhexidine allergy among HCW with itching, urticarial rash and rhinitis, confirming the diagnosis in 4 (7.7%) of the 52 patients investigated (14).

The three cases described in 2013 did Toholka et al. report a case of contact allergy sensitization, confirmed by Patch Tests, in 10 (2%) out of 541 HCWs, a higher rate than previously documented (27).

In 2016, Ibler et al. studied a sample of 120 HCWs by performing allergy tests; chlorhexidine-mediated delayed-type and immediate-type hypersensitivity was found in 1 participant (<1%). However, they concluded that, owing to widespread exposure, chlorhexidine should be included in occupational allergy investigations in HCWs (8).

Recently, Vu et al. described a case of immediate hypersensitivity to chlorhexidine in an endoscopy technician, with a history of urticaria and respiratory symptoms, which was confirmed by means of SPTs (29).

The literature reports very few cases of allergic reactions in professional categories other than HCWs, such as agricultural workers (9).

Diagnosis is usually based on the subject’s clinical history, SPTs and serum-specific IgE in cases of clinical immediate-type manifestations (14). However, in cases of severe reaction, skin tests are deemed unethical and BAT may be carried out: this is another reliable in vitro diagnostic tool, though not usually available (2, 3).

In our case report, diagnostic procedures did not include SPTs for antiseptics because of the severity of the reaction and the fact that sIgE, measured three months after the reaction, showed low values. By contrast, positive BAT results confirmed the suspicion of an immediate chlorhexidine-induced hypersensitivity reaction and excluded a role of other disinfectants, which proved negative. The contradictory results yielded by BAT and sIgE for chlorhexidine may have been due to the different sensitivity of the two tests; indeed, basophil activation is triggered by the cross-linking of membrane IgE even when total and sIgE are low, while sIgE are detected in serum with a great dilution factor.

**Conclusions**

Hypersensitivity to chlorhexidine appears to be a rare phenomenon, though it may be overlooked and hence under-reported. In view of the widespread use of chlorhexidine to control infections in health-
care settings, and the consequent high exposure of HCWs, the present case report underlines the importance of better investigating individual and environmental risk factors that may lead to chlorhexidine sensitization among employees.

As anaphylaxis and other severe systemic allergic reactions have serious consequences for both the health and productivity of workers, this issue needs to be more thoroughly investigated in order to acquire further knowledge for use in planning proper prevention strategies.

Appropriate health surveillance programs in these occupational settings should consider the implications of exposure to chlorhexidine in order to prevent life-threatening events. In this regard, it is noteworthy that workers who are sensitized to specific allergens in the workplace may also develop anaphylaxis outside (22, 31), creating further difficulties for the proper management of this severe clinical picture. Adequate information should be made available to the medical community, which generally has scant knowledge of the side effects of chlorhexidine and its potential severe adverse reactions (25).

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