Chlorhexidine and hypersensitivity reactions in dentistry

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VERIFIABLE CPD PAPER

IN BRIEF

- Describes the history of chlorhexidine use in medicine and dentistry.
- Highlights the spectrum of reported hypersensitivity reactions to chlorhexidine.
- Reports two cases of death due to anaphylaxis following the use of chlorhexidine in post-extraction tooth socket care.

PRACTICE

Immunological reactions to chlorhexidine, including allergy (Type I hypersensitivity) and allergic contact dermatitis/stomatitis (Type IV hypersensitivity), have been recognised for many years. This potential safety issue, however, is not well known within dentistry. The purpose of this paper is to alert dentists and dental care professionals to the potential of chlorhexidine in causing hypersensitivity reactions and to consider this possibility if unexplained hypersensitivity reactions occur.

INTRODUCTION

In the 1970s, seminal studies on the value of chlorhexidine mouthwash in the control of plaque and gingivitis were undertaken.^{1,2} Following these studies, 0.1–0.2% chlorhexidine mouthwash has become a frequently recommended or prescribed treatment in the management of gingivitis. Studies have shown its benefit over other potentially useful plaque inhibiting agents and indicated specific situations in which chlorhexidine is of particular benefit.³ As well as being available in a mouthwash form, chlorhexidine is also available in other vehicles for use in oral healthcare including toothpastes, sprays and gels. Common side effects, such as staining of teeth are well recognised; however, rarer, but potentially more severe side effects including hypersensitivity, are less well known.

CHLORHEXIDINE HYPERSENSITIVITY AND MEDICAL PRODUCTS

For many years, chlorhexidine-containing products have also been used in other areas of medicine because of chlorhexidine's beneficial effects as a topical antimicrobial agent. These products include antiseptic

skin creams and disinfectants used to prepare the skin for surgical procedures. In the early 1990s, chlorhexidine also began to be incorporated into the composition of medical devices including intravenous catheters, topical antimicrobial skin dressings and implanted antimicrobial surgical mesh.⁴

From use in all of these medical applications, it has become apparent that chlorhexidine has the potential to produce hypersensitivity reactions. Hypersensitivity reactions are generally known to occur in four main forms, I–IV, with Type I (immediate and mediated chiefly by immunoglobulin E) and Type IV (delayed and mediated by the cells of the immune system) being the reactions of greatest concern in the orofacial region.

The Type IV hypersensitivity reaction of contact dermatitis to chlorhexidine has been reported in both adults and children with confirmation by patch testing in many cases.^{5–7} This delayed type of hypersensitivity has most frequently followed the use of chlorhexidine-containing topical medicinal creams used to treat inflamed skin. It has also followed the use of cosmetic products containing chlorhexidine.

Type I hypersensitivity reactions have been reported especially where chlorhexidine has been used topically, intra-urethrally, and with chlorhexidine-impregnated catheters. Incidents of this immediate allergic type of hypersensitivity have been reported from all over the world, with the reactions reported ranging from localised urticaria to life-threatening anaphylactic shock.^{8–11} Details of how to

Table 1 Mild allergy – signs, symptoms and management¹³

Key symptoms and signs of mild allergy
Urticaria and rash, particularly of chest, hands and feet
Rhinitis, conjunctivitis
No difficulty breathing
Key management principles of mild allergy
Assess the patient
Give oral antihistamine (for example, chlorphenamine 4 mg tablet or loratadine 10 mg tablet in adults. Refer to BNF or BNFC for child doses)
Reassess the patient. If severe reaction developing, treat as for anaphylaxis
Refer patient to their general medical practitioner

manage mild Type 1 hypersensitivity (allergic) reactions and anaphylaxis are given in Tables 1 and 2.^{12,13} The true prevalence of these reactions remains unknown. In the medical literature, reactions have mainly been recorded in case reports with these cases falling into three broad categories.¹⁴

Type I hypersensitivity reactions have been reported when chlorhexidine has been applied to damaged skin surfaces.^{8,10,14} These instances include wounds and burns or when the skin was cut in surgical procedures and a chlorhexidine containing product had been used in the preparation of the skin. Anaphylactic reactions have been reported. There have also been a few cases in which chlorhexidine use on unbroken skin has also led to immediate type hypersensitivity reactions.¹⁴ These include when chlorhexidine has been

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applied to pre-existing hand dermatitis, acne or to erythematous skin.

Type I hypersensitivity reactions, including anaphylaxis, have been reported when chlorhexidine has been applied to mucous membranes.^{11,14–16} In the majority of cases, these have been associated with chlorhexidine-containing gels and lubricants inserted into the urethra before catheterisation or cystoscopy. Other cases have been reported following chlorhexidine lubricant applied intra-vaginally before gynaecological examination and chlorhexidine-containing ophthalmic wash solution.

Type I hypersensitivity reactions have been reported when chlorhexidine has been impregnated into central venous catheters.^{14,17,18} In 1996, such catheters were introduced into practice and within the next few years, there were reports of patients experiencing anaphylactic-like adverse effects. Reports came from several countries, but the majority were from Japan. It is not clear why the majority of these reactions occurred in the Japanese population. Possible explanations include a genetic predisposition or an increased exposure to chlorhexidine-containing products resulting in heightened sensitivity. The catheter was subsequently withdrawn from use in Japan, and the United States Food and Drug Administration issued an alert concerning potential hypersensitivity reactions to chlorhexidine-impregnated medical devices.^{4,17} The alert recommended that if a patient exhibited an unexplained hypersensitivity reaction, then steps should be taken to determine whether chlorhexidine was used or not.

Confirmation of Type I hypersensitivity reactions to substances is usually undertaken by skin prick testing or identification of specific IgE antibodies in the blood. In many of the reported cases of chlorhexidine allergy, positive reactions on skin prick testing with weak concentrations of chlorhexidine have been found.⁸ Chlorhexidine specific IgE antibodies have been identified in the serum of affected patients, which lends further evidence that a true Type I hypersensitivity reaction has occurred in these individuals.⁸

CHLORHEXIDINE HYPERSENSITIVITY AND DENTAL PRODUCTS

Chlorhexidine is most commonly used in dentistry as a mouthwash. In the

early 1970s, many studies were carried out looking at the utility of chlorhexidine mouthwash as part of dental care. Radiolabelling of chlorhexidine was used to identify the retention and distribution of 10 ml of a chlorhexidine 0.2% mouthwash used in healthy volunteers. It was found that an average of 4% of the compound was swallowed by the adults studied and an average of 30% retained in the mouth.¹⁹ There was a rapid fall in the chlorhexidine concentration found in the mouth over the first few hours, but with some activity still present after 24 hours. While chlorhexidine appeared to be a poorly absorbed drug, radiolabelled chlorhexidine was detected in the kidney and liver in animal studies, indicating some absorption had occurred.²⁰ In 1971, a study looked at the side effects of chlorhexidine mouthwashes in a group of 50 soldiers over a period of four months.²¹ The study found some cases where chlorhexidine mouthwash caused irritation and damage to the oral mucosa with resultant chemically-induced trauma. The frequency of this side effect appeared to increase with increasing chlorhexidine concentration.

In the early 1970s, no cases of sensitisation to chlorhexidine used in the mouth had yet been observed.²¹ Since then, immunological reactions to chlorhexidine when used in the mouth have been infrequently documented in the medical and dental literature. Allergic contact stomatitis (Type IV hypersensitivity) has been reported following the use of chlorhexidine-containing mouthwash with the hypersensitivity confirmed by patch testing.⁷ However, in other reports of possible hypersensitivity relating to chlorhexidine-containing products used in the mouth, it is sometimes unclear as to which type of immunological response is actually occurring.²² Rarely Type I allergy has been reported following use of chlorhexidine in the mouth, or on the lips. In one case, confirmed by positive skin prick testing, anaphylactic symptoms occurred following treatment with antiseptic dental gel containing 1% chlorhexidine gluconate.²³ In another case confirmed by skin prick testing, urticarial skin lesions followed the use chlorhexidine gluconate-containing mouthwash.²⁴ In a further case, generalised urticaria, flushing, cough and general fatigue followed

Table 2 Anaphylaxis – signs, symptoms and management^{12,13}

Key symptoms and signs of anaphylaxis may include
Facial flushing, swelling and paraesthesia
Generalised urticaria or itching
Wheezing, stridor or difficulty breathing
Abdominal pain
Sense of impending doom
Rapid, weak or impalpable pulse
Falling blood pressure
Key management principles of anaphylaxis
Assess the patient using an ABCDE approach
Call ambulance
Secure the airway and give 100% oxygen (10–15 litres per minute flow rate)
Lay patient flat and raise legs to support blood pressure
Administer 0.5 ml of 1:1000 adrenaline (adrenaline) in adults via intramuscular injection and repeat at 5 minute intervals if needed. (For children, child 6–12 years give 0.3 ml of 1:1000 adrenaline, child less than 6 years give 0.15 ml of 1:1000 adrenaline)
Monitor patient and if cardiac arrest occurs, start basic life support immediately

shortly after an upper lip injury was disinfected with 0.05% chlorhexidine gluconate.¹⁶ The patient subsequently showed a positive response to an intra-dermal test.

Recently we have become aware of two cases of anaphylaxis in the UK, thought to be triggered by chlorhexidine products used in dental practice – both of which resulted in fatalities. Both cases appear to have involved the use of chlorhexidine in the treatment of tooth sockets after dental extraction. It is unclear how much the application of chlorhexidine to an 'open wound' influenced the nature and severity of the allergic reactions that ensued, but it is likely to have increased the amount of chlorhexidine absorbed into the blood stream compared to a topical application on intact oral mucosa.

Case one

The death of a 63-year-old male patient following dental treatment in Penrith, UK, was considered at a coroner's inquest in February 2011, the death having taken place in October 2009.²⁵ The coroner returned a verdict of accidental death due to an allergic reaction. The inquest heard

expert evidence that there was a 95% certainty that the allergic reaction had been to chlorhexidine. The patient had a respiratory arrest and died in hospital without regaining consciousness, despite the dental practice staff offering the patient the best possible treatment for his anaphylaxis, including the administration of adrenaline by injection, as reported at the inquest. Chlorhexidine had been used to irrigate a tooth socket and other causes for the anaphylaxis were effectively excluded.

Case two

The death of a 30-year-old female patient following dental treatment in Brighton, UK, was considered at a coroner's inquest in September 2011, the death having taken place in February 2011.^{26,27} The coroner returned a verdict of death by medical misadventure, with the death being due to anaphylaxis, most likely to a dental mouthwash containing chlorhexidine. Once again, the mouthwash had been used in the clinical situation of treating a socket days after a tooth had been extracted. The coroner reported that, '*the failure to diagnose anaphylactic shock was regrettable but understandable in the light of the extraordinary speed of the illness*'.

CHLORHEXIDINE HYPERSENSITIVITY AND HEALTHCARE WORKERS

The use of chlorhexidine within medicine is increasing. The recent heightened awareness of hospital acquired infections has encouraged frequent hand decontamination among healthcare workers. Many of the products used contain chlorhexidine and concern has been raised that the incidence of chlorhexidine allergy will increase in parallel with increased exposure to chlorhexidine. There are concerns that the incidence of chlorhexidine allergy may follow the epidemiological history of latex allergy. Although delayed hypersensitivity to latex is long established, immediate hypersensitivity to latex only first appeared in the medical literature in 1979.²⁸ Following that report, the number of reported cases of allergy to latex increased alarmingly, with peak incidence in the 1980s and 1990s. This was attributed to the greatly increased use of latex in healthcare, especially latex gloves, as well as greater awareness of the problem.²⁹ After patients with spina bifida, healthcare

workers were found to have the second highest risk of developing latex allergy. Following the ban on the use of powdered latex gloves, the incidence of latex allergy in all groups, including healthcare workers, has fallen markedly.³⁰

Several studies have attempted to look at the incidence of chlorhexidine hypersensitivity susceptibility among healthcare workers. In 2003, Danish healthcare workers were investigated with skin prick testing (for Type I hypersensitivity), patch testing (for Type IV hypersensitivity) and by questionnaires.³¹ There were no positive tests in 104 participants tested and no histories of suspected hypersensitivity reactions to chlorhexidine. More recently, in 2009, British healthcare workers in a district general hospital who thought they might be allergic to chlorhexidine were investigated by skin prick testing and identification of positive specific IgE to chlorhexidine.³² Four cases were positive on testing. These were the first reports of confirmed occupational IgE mediated chlorhexidine allergy in healthcare workers. In all four cases there was a history of itching and urticaria of the skin after using chlorhexidine-containing handwash. Two of the cases were also found to be allergic to latex as well. None had had a more serious anaphylactic reaction. Where identified, chlorhexidine hypersensitive healthcare workers should use non-chlorhexidine hand washes such as povidone iodine or 70% ethanol-based products. For such healthcare workers, chlorhexidine-containing household products such as Savlon® antiseptic should be avoided and chlorhexidine should not be used at all during their clinical practice.

It is unclear whether the incidence of chlorhexidine-related allergy is increasing in healthcare workers or in the population in general. It is clear, however, that hypersensitivity can occur to this widely used antiseptic, and dental healthcare professionals need to be aware of this possibility. In January 2012, the UK Medicines and Healthcare products Regulatory Agency released a drug safety update to all healthcare workers on the potential for chlorhexidine to induce hypersensitivity, as a reminder of this risk.³³ Chlorhexidine is a very commonly used product in many areas of dental practice and it is easy to forget that such everyday products have

the potential to cause serious adverse reactions. We hope that this paper also serves as a reminder to practitioners of this very rare, but important risk. The circumstances of the recent fatalities in a UK dental setting where chlorhexidine appears to have been used in the management of patients after the extraction of teeth may suggest that, like other situations in medicine and surgery described previously, 'open wounds' may increase the likelihood of allergic reactions occurring.

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