

PHARMACOLOGY

Chlorhexidine allergy: raising awareness about rare but potentially life-threatening reactions

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Clorhexidine (CHX) is an antiseptic agent commonly used in many areas of clinical dentistry. Despite the ubiquity of CHX, dental products containing this agent can cause various hypersensitivity reactions that range in severity from type IV, delayed hypersensitivity (usually manifesting as urticaria and dermatitis or fixed drug eruptions), to type I, which has serious and life-threatening consequences (immediate hypersensitivity and anaphylaxis).¹⁻⁶ The prevalence of CHX hypersensitivity is unknown; it is considered rare, but case reports in recent years have highlighted the need for awareness, especially recognition that allergic contact dermatitis may predispose patients to more serious type I reactions on subsequent CHX exposure.^{1,5-8}

Given the number of dental products that contain CHX (such as mouthwashes, toothpastes, gels, periodontal chips, cavity cleansers, varnishes, and hand sanitizers), it is likely that hypersensitivity reactions following the use of CHX in the dental setting will continue to increase.^{5,9,10} In 2014, the UK Medicines and Healthcare Products Regulatory Agency updated an earlier warning to healthcare providers about the risk of anaphylactic reactions due to CHX allergy.^{11,12} More recently, the increased prevalence of CHX allergies was highlighted by a Drug Safety Communication published by the US Food and Drug Administration (FDA) in February 2017.¹³

In this alert, the FDA warned of rare but potentially serious allergic reactions from CHX-containing products, stating that “the number of reports of serious allergic reactions to these products has increased over the last several years.”¹³ The basis of the FDA Drug Safety Communication was several recent reports of anaphylaxis, including 2 deaths.

History of CHX in medicine and dentistry

CHX was developed in the 1940s by Imperial Chemical and was first approved for use in 1954 in the United Kingdom, soon becoming available in other countries.^{5,14,15} CHX mouthrinse was introduced in 1969 by Løe, and subsequent studies demonstrated that 2 daily mouthrinses with 0.2% CHX gluconate in conjunction with mechanical oral hygiene measures prevented plaque formation and the development of gingivitis.¹⁶⁻¹⁸ During a 2-year study by Løe et al, no adverse health effects were observed among users, and the only negative outcome was tooth staining.¹⁸

A CHX gluconate mouthrinse was approved for use in the United States by the FDA in 1986, and Procter & Gamble began selling the agent under the brand name Peridex.^{19,20} Although 0.2% CHX gluconate mouthrinse was available in Europe during this time, Peridex was approved at the 0.12% concentration, primarily to mitigate brown tooth staining. In 1986, Peridex also became the

first oral healthcare product to receive the American Dental Association Council on Dental Therapeutics’ seal of acceptance for control of plaque and gingivitis.^{20,21} The studies by Procter & Gamble that helped to bring Peridex to market showed limited tooth staining at the reduced concentration but also listed other common side effects following oral use of this product, including increased calculus formation and alterations in taste.^{20,22} CHX is included in the World Health Organization’s *WHO Model List of Essential Medications*.²³

Currently in dentistry, CHX is used for the prevention of primary and secondary gingivitis, periodontal disease, and caries; surgical and endodontic irrigation; management of postoperative sensitivity; and cavity disinfection. In addition to the gluconate mouthrinse formulation, which became generic in 1994, CHX can now be found in gels, sprays, toothpastes, discs, chips, varnishes, sugar-free chewing gum, and hand sanitizers.^{15,24,25}

Pharmacology of CHX

CHX is a synthetic bisbiguanide topical antiseptic with a symmetric molecular formula consisting of 4 chlorophenyl rings and 2 biguanide groups connected by a central hexamethylene bridge (Figure).^{24,26} It is a broad-spectrum antimicrobial exhibiting concentration-dependent bactericidal and bacteriostatic effects. CHX is effective against gram-positive and gram-negative bacteria, fungi, and some

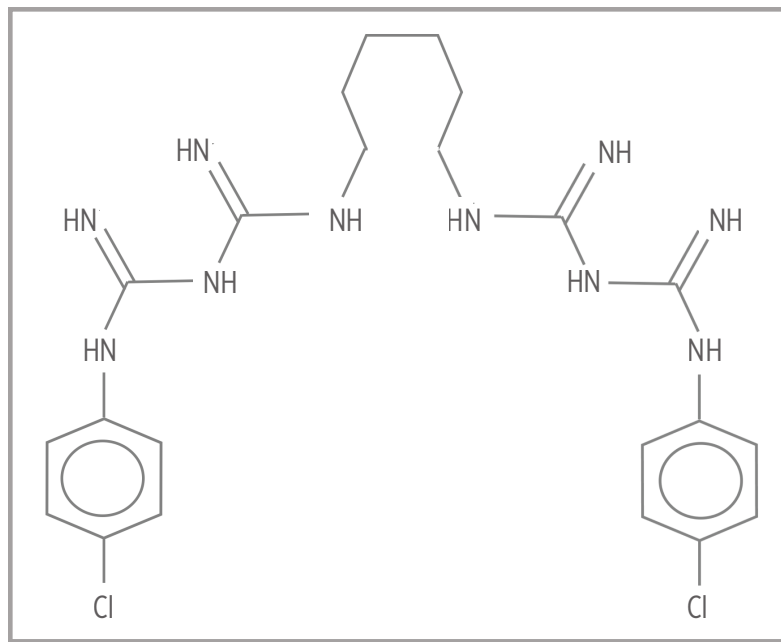


Figure. Chemical structure of chlorhexidine.

viruses. Its killing effectiveness is principally due to the positively charged CHX molecules (cations), which are attracted to negatively charged cell membranes. At lower concentrations, CHX is bacteriostatic and acts by altering cellular osmotic balance and promoting the release of low-molecular weight molecules.^{25,26} At higher concentrations, CHX binds to microbial cell walls, thus altering the membrane integrity and leading to leakage of the intracellular contents.^{15,25,27}

Its substantivity is another major advantage of CHX in the oral environment. CHX adheres to both oral hard and soft tissues by binding to mucins, the proteins responsible for the salivary film over teeth and mucosa.¹⁰ This property allows CHX to remain present in the oral environment and have antimicrobial and antiplaque effects that last 8-12 hours.²⁴⁻²⁶ The antimicrobial action of CHX on the skin has been documented to last up to 48 hours, and therefore CHX is commonly used as a topical antiseptic and surgical scrub for perioperative prophylaxis.²⁸⁻³⁰ When CHX is used as an endodontic irrigating solution, there is evidence that its substantivity can last days or weeks, with Rosenthal et al reporting antimicrobial activity in root canal dentin for up to 12 weeks.^{31,32}

CHX that is swallowed or is absorbed through mucous membranes undergoes

minimal metabolic changes and is excreted in the feces.³³ CHX-containing mouthrinses are listed as FDA Pregnancy Category B, indicating that animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate, well-controlled studies in pregnant women. CHX chips are listed as FDA Pregnancy Category C.^{24,34-36} Because CHX is poorly absorbed through mucous membranes, use during lactation is not contraindicated; however, no data are available on the excretion of CHX in breast milk following oral rinsing.^{24,33} Regardless, several sources list CHX as compatible with breastfeeding.^{35,37,38}

Reports of allergic reactions to CHX

The first report of an allergic reaction to CHX was published in 1965 and involved a 72-year-old woman whose skin was swabbed with CHX prior to venipuncture.^{14,39} The first reported case of anaphylaxis was published in 1984 and involved a 9-year-old boy who received a topical application of CHX solution during a surgical operation.^{6,40} Since these early cases, reports of CHX-induced allergic reactions have increased in both the medical and dental literature.^{5,6,41-49}

In 1986, Ohtoshi et al reported a case of CHX-induced anaphylaxis in a

24-year-old man whose abraded skin was treated with a 0.5% CHX solution.⁵⁰ Within 10 minutes of CHX application, the patient's symptoms included urticaria and hyperemia. Within 1 hour, the patient was hypotensive and had lost consciousness. Emergency treatment included epinephrine and corticosteroids, and full recovery occurred over the following 48 hours. Besides this case, Ohtoshi et al discussed more than 30 other cases of anaphylaxis occurring in the previous 5 years.⁵⁰

Several literature reviews and case series have highlighted CHX-induced allergies.^{1,5,7,8} A literature review by Silvestri & McEnery-Stonelake described 58 cases of allergic contact dermatitis due to CHX, and in 5 of the patients an oral mucosal sensitization via a mouthrinse was the initial exposure.⁵ Bubenhofer et al described 16 cases of CHX allergy: 13 of these patients had an immediate reaction and 7 were anaphylactic with hypotension.¹ One-third of the documented reactions occurred in the dental office. The authors speculated that CHX-induced allergic reactions are not well recognized because CHX is often an adjuvant in a product rather than the main constituent. Because CHX appears in many medical and dental products, and because allergic reactions are rare and their prevalence is not clearly understood, the possibility of hypersensitivity reactions may be underestimated.^{1,8,10}

Several cases of CHX hypersensitivity have been reported in the dental literature. Moghadam et al reported a skin reaction following the use of CHX mouthrinse after periodontal surgery.³ The reaction manifested as pruritus and erythematous rashes on the palms of the hands and soles of the feet. Pemberton & Gibson reported 2 cases of anaphylaxis following CHX irrigation of extraction sockets; in both cases the patients died.² Sharma & Chopra described a case where a 19-year-old woman was prescribed CHX mouthrinse for bleeding gingivae.²⁷ After using the rinse 2 times over a 24-hour period, the patient presented with urticaria over her neck, face, arms, and back. No oral changes were observed. Her allergic reaction to CHX was later confirmed with skin testing.

Recently, the first case of CHX-induced anaphylaxis of an oral healthcare provider in the workplace was published.¹⁰ Toletone et al described a case in which a dentist experienced rapid onset of acute and diffuse urticaria and loss of consciousness.¹⁰ He was immediately treated with epinephrine and steroids. Interestingly, the dentist had previously experienced 2 episodes of transitory loss of consciousness, but the results of skin prick testing for common allergens (including latex) were negative. Three months following the anaphylactic reaction, the dentist was tested for CHX allergy via an immunoglobulin E and basophil activation test, and a CHX allergy was confirmed. The mode of exposure to CHX was believed to be contact with aerosol during the cleaning and disinfection of hard surfaces with a CHX-containing antiseptic/disinfectant. Toletone et al also completed a literature review showing 14 other cases of CHX allergy in healthcare workers, including nurses, nursing students, a midwife, and an endoscopy technician.¹⁰ Reactions included itching, urticaria, dermatitis, pruritic eruptions, papular eruptions, asthma, coughing, dyspnea, and wheezing.

Clinical implications

CHX is a commonly used antiseptic in medicine, dentistry, and consumer products. Hypersensitivity reactions are rare but are well documented; type IV delayed reactions are more common than type I immediate hypersensitivity and anaphylaxis.⁶ Delayed-type hypersensitivity may be characterized by urticaria, dermatitis, rhinitis, and conjunctivitis without difficulty breathing.^{2,3,6} An acute onset of type I anaphylactoid reactions requires immediate activation of an office's emergency response plan.

Pemberton concluded that type I immediate hypersensitivity and anaphylaxis due to CHX have been most commonly associated with 3 circumstances: use of CHX on damaged skin surfaces, including wounds and burns; application of CHX to mucous membranes outside the mouth (including the use of CHX-containing products on the urethra, vagina, eye, and nose); and insertion of CHX-impregnated medical devices (such as central venous catheters).⁶ It is important

to remember that several reports of anaphylaxis included previously documented mild urticarial symptoms. Of greater concern is that in some cases of CHX-induced anaphylaxis, patients had already undergone allergy testing with negative results.^{1,14}

Oral healthcare providers must be aware of the potential for rare but potentially life-threatening allergic reactions to CHX. Because hypersensitivity reactions to CHX mouthrinses have manifested outside of the oral cavity, oral healthcare providers must be vigilant to ask patients about any previous exposure to CHX and adverse reactions prior to use. Any patient reporting urticaria or dermatitis anywhere on the body should be referred to an allergist for testing.⁵

Since CHX is commonly used in many settings, the chances of exposure and potential sensitization are likely increasing. This is analogous to healthcare providers' past experience with the overuse of latex-containing products, which resulted in an increased prevalence of latex allergies.⁵¹ Heightened awareness can help oral healthcare providers recognize the signs and symptoms of CHX allergy and prevent more serious immediate and anaphylactic reactions.

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Disclaimer

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