

Perioperative chlorhexidine allergy: Is it serious?

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Abstract

Chlorhexidine is an antiseptic agent, commonly used, in many different preparations, and for multiple purposes. Despite its superior antimicrobial properties, chlorhexidine is a potentially allergenic substance. The following is a review of the current evidence-based knowledge of allergic reactions to chlorhexidine associated with surgical and interventional procedures.

Key words: Allergy, anesthesia, complications, chlorhexidine, perioperative

Introduction

Chlorhexidine is an antiseptic agent, cationic polybiguanide, commonly used, in many different preparations, and for multiple purposes primarily as a skin and wound disinfectant but also in cosmetics and several pharmaceutical products, such as in eye drops, mouthwashes, creams, hand rinses, toothpaste and deodorants.^[1,2] Chlorhexidine salts dissociate with release of positively charged chlorhexidine cations at physiological pH. The bacteriostatic and bactericidal actions of chlorhexidine are concentration-dependent, with disruption of the bacterial membrane and cell death occurring at high concentrations. The use of chlorhexidine is recommended in various clinical settings secondary to its activity against a broad range of organisms: Gram-negative and gram-positive as well as facultative aerobes/anaerobes and yeast.^[3] Chlorhexidine has been used and recommended as per infection control guidelines and figures on the World Health Organization’s list of essential medicines.^[4] It is applied and is extremely useful in several poor, underserved areas

for disinfection of the umbilical cord in newborns. However, despite its superior antimicrobial properties, chlorhexidine is a potentially allergenic substance. The following is a review of the current evidence-based knowledge of allergic reactions to chlorhexidine associated with surgical and interventional procedures.

Review of Studies and Reports

Relevant, peer-reviewed original research articles, reviews and reported cases between 1980 and 2014, as identified in Medline/PubMed using the keywords anaphylactoid, anaphylaxis, and chlorhexidine were reviewed.

During anesthesia, different mediators may be implicated in anaphylactic/anaphylactoid responses such as: IgE in type I hypersensitivity mechanisms, IgA, immunocomplexes, complement activated by an alternative pathway, tryptase, and histamine. Diagnostic methods include skin tests, challenge, histamine release test, human basophil optical degranulation test, and ImmunoCAP.^[5] Flow cytometric allergen stimulation tests show promise in differentiating allergic from idiosyncratic pseudo allergic reactions.^[6] An increase of tryptase concentration in the serum confirms the diagnosis of an anaphylactic reaction, and triggers may be evaluated and identified by skin tests, intradermal injection, or serologic testing. These tests are useful in eliminating allergens and selecting alternatives during subsequent anesthesia administration, in order to avoid complications, mortality and morbidity.^[7]

Chlorhexidine has been reported to cause allergic reactions in sensitized patients. Dermatitis or stomatitis caused by chlorhexidine-containing topical medicaments has

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been documented.^[8,9] Studies showed that anaphylaxis associated with invasive, interventional and surgical procedures include neuromuscular blocking agents, natural rubber latex, antibiotics, and induction agents as the most common causes. Colloids, opioids, and radio contrast media are less frequent and probably account for <10% of all reactions. The more recent and newer agents used perioperatively, and reported as implicated in anaphylaxis include isosulfan blue and chlorhexidine.^[6] A positive patch reaction to chlorhexidine was seen in 36 (0.47%) dermatology patients with suspected contact allergy. Furthermore, four cases of occupational IgE-mediated allergy to chlorhexidine were identified in the UK.^[10] Hypersensitivity reactions to chlorhexidine have included allergic contact dermatitis, pruritus, vesicle formation, urticaria, dyspnea, and anaphylactic shock. The precise incidence of chlorhexidine allergic reactions and the associated morbidity and mortality remain unknown. Patch testing using chlorhexidine has revealed positive reactions in more than 2% of patients tested. In eczema patients, the rate may be as high as 5%.^[11] Since chlorhexidine is the standard skin disinfectant used before surgery or invasive procedures, the potential for developing allergy to chlorhexidine is significant, especially under anesthesia. Four patients with severe allergic reactions to chlorhexidine associated with surgery and general anesthesia have been reported. Symptoms manifested 20-40 min into the procedure, and all patients required administration of adrenaline. The four patients, subsequently, tested positive for chlorhexidine on skin testing. A history of minor symptoms like rashes in relation with previous invasive procedures or surgeries was present in all of these patients.^[12] Another report described six patients who had anaphylactic reactions attributed to chlorhexidine during surgery. These patients were exposed to chlorhexidine in gels, swabs and catheters. On detailed assessment, five of the six patients demonstrated a previous history of reactions on re-exposure to chlorhexidine. All six patients had elevated specific IgE to chlorhexidine. Skin prick test with chlorhexidine was performed in four of the six patients and was found to be positive.^[13] A retrospective analysis of patients referred from 2007 to 2011 to a university allergy center with the suspicion of an allergic reaction associated with general anesthesia revealed that a diagnosis of IgE-mediated reaction was established in 63.9% of cases. The most common agents involved were neuromuscular blocking agents (61.8%), antibiotics (14.5%), latex (9.2%) and chlorhexidine (5.2%).^[14]

Chlorhexidine allergy is IgE-mediated and measurement of specific IgE and histamine release are good adjuncts to skin testing to support the diagnosis of chlorhexidine allergy

in patients with clinical history suggesting sensitivity to chlorhexidine.^[15] Investigations of allergic reactions during anesthesia ranging from mild to severe would follow a standard step-by-step protocol of skin testing and *in vitro* testing. Blood samples for tryptase analysis are drawn at the time of the allergic reaction, and a control sample is drawn together with samples for specific IgE analysis 2-4 weeks after the allergic reaction. Subsequent skin testing comprises both prick tests and intradermal tests in most cases. Patients are tested with all potential allergic substances exposed to, including antibiotics, colloids, latex and chlorhexidine.^[16] The incidence of anaphylaxis to vital dyes and chlorhexidine has been reported as increasing.^[17] In the presence of an allergic reaction, investigation should include screening for chlorhexidine in all patients as exposure to both these agents is common and allergic reaction to this substance may be overlooked.^[18]

In a study including patients with leg ulcers, patch testing to chlorhexidine performed with chlorhexidine gluconate aq., and chlorhexidine acetate 1% aq., reported that 39/297 of patients showed positive reactions to one of these compounds or to both, 36 positive reactions to chlorhexidine acetate were observed, in contrast to 18 reactions to chlorhexidine gluconate. In 22 of the 39 patients with positive reactions, the results were considered relevant, since these patients had developed an eczematous reaction in the area where a chlorhexidine compound was used, and discontinuing chlorhexidine resulted in improvement of the reaction. It is of note that in 10 of these 22 symptomatic patients, the diagnosis would have been missed if the gluconate was the only compound used for testing, while the chlorhexidine acetate test failed to diagnose two patients. In patients without leg ulcers, inconclusive patch test readings (i.e., irritant reactions or weak positive reactions) were found in 17% with chlorhexidine acetate 1% aq., compared to 5% with chlorhexidine gluconate 1% aq., implying a high degree of irritant potential of the acetate 1% aq. Some positive reactions would be lost if chlorhexidine gluconate 1% aq., only is used for patch testing, therefore, the authors suggested that further testing with chlorhexidine acetate 1 and 0.5% aq., should be performed, in parallel with chlorhexidine gluconate 1% aq., in order to establish appropriate test concentration.^[19]

On a molecular basis, two molecules of chlorhexidine form the symmetrical molecule of chlorhexanide while the interior structure of alexidine (that is excluding the terminal 2-ethylhexyl groups) is identical to part of the chlorhexidine molecule. Chlorhexanide and alexidine, the structures of which each comprise part of the chlorhexidine molecule, showed significant inhibition of the binding of IgE antibodies to chlorhexidine; however, neither compound was as potent an inhibitor as chlorhexidine itself. It

seems that the whole chlorhexidine molecule is complementary to the IgE antibody combining sites and that the 4-chlorophenol, biguanide and hexamethylene structures together comprise the allergenic determinant.^[20]

Recommendations

The true incidence of chlorhexidine allergic reactions and their associated morbidity and mortality remains unknown. It is recommended that centers investigating patients with reactions during anesthesia and surgery should routinely include testing for chlorhexidine allergy.^[13, 21] Anaphylaxis during surgical and interventional procedures may be difficult to evaluate because of the rapid, successive use of multiple drugs. A detailed history, and careful analysis of anesthetic records and diagnostic tests such as determination of chlorhexidine specific IgE, mast cell tryptase and skin tests may be performed to ensure a complete evaluation. Any suspected hypersensitivity reaction during anesthesia must be extensively investigated to confirm the nature of the reaction, to identify the responsible drug, and to provide recommendations for future anesthetic procedures. Tryptase assay at the time of the reaction has to be implemented by thorough investigations carried out weeks later: Prick tests and intradermal tests, quantification of specific IgE, histamine release test or cytometric analysis of basophile activation.^[17] An informed guess is not a reliable way of determining the cause of a supposed allergic reaction during anesthesia and may put a significant number of patients at unnecessary risk. Some patients may be labeled with a wrong allergy, leading to unnecessary warnings against harmless substances, and some patients may be put at risk of subsequent re-exposure to the real allergen. Patients with suspected allergic reactions during anesthesia should be referred for investigation, whenever possible.

Conclusion

Hypersensitivity reactions to chlorhexidine are diverse and comprise allergic contact dermatitis, pruritus, vesicle formation, urticaria, dyspnea, and anaphylactic shock.^[15] Principal sources of chlorhexidine contact sensitization are chlorhexidine-containing corticosteroid creams, skin disinfectants and oral hygiene products. There are many reports of allergic reactions, including anaphylaxis, following exposure to chlorhexidine. Reactions may occur via contact with the skin and mucous membranes or from catheters treated with an antibacterial agent. In the surgical patient, allergy to chlorhexidine may be more prevalent^[12] with possibility of underreporting of cases due to the lack of suspicion toward this substance.

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