

A Case of Severe Anaphylaxis to Polyhexanide: Cross-Reactivity between Biguanide Antiseptics

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Established Facts

- Polyhexanide and chlorhexidine belong to the biguanide group of antiseptics and share the hexamethylene biguanide structure motive.
- While chlorhexidine is an established cause of anaphylaxis, only 3 cases of anaphylaxis to polyhexanide have been described before.

Novel Insights

- Cross-reactions between polyhexanide and chlorhexidine are probable.
- Structurally different antiseptics should be favored in a patient with either allergy.
- Polyhexanide might be an emerging allergen.

Keywords

Anaphylaxis · Antiseptic · Biguanide · Chlorhexidine · Cross-reactivity · Polyhexanide

Abstract

We present the case of a 77-year-old female patient who suffered from severe anaphylaxis during wound care. Allergologic evaluation yielded specific IgE antibodies to chlorhexidine, but anaphylaxis to chlorhexidine was not congruent with the patient history and dermal provocation tests. However, skin prick tests provided evidence for a sensitization to polyhexanide that was further supported by the detection of specific IgE antibodies to polyhexanide, the results of basophil activation tests and IgE inhibition analysis. We presume

cross-reactive IgE antibodies binding to both biguanide antiseptics and identified polyhexanide as the likely cause of the anaphylactic reaction. We recognize polyhexanide as an emerging allergen that has to be considered as a cause of anaphylaxis.

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Introduction

Polyhexanide belongs to the biguanide antiseptics and is also a component of some surface disinfectants, wound gels and cosmetic products. Likewise, chlorhexidine is assigned to the biguanide group. Anaphylaxis to chlorhexidine has widely been described. The first case reports of

anaphylaxis to chlorhexidine were published in the 1980s in Japan [1]. Sixty-five cases of anaphylaxis to chlorhexidine have been published between 1994 and 2013 [2], and an allergy to chlorhexidine has been proven causative in 10% of 228 cases of unclear perioperative anaphylactic reactions [3].

In contrast to chlorhexidine which has accordingly been established as a progressively important cause of anaphylaxis, to our knowledge there have only been 3 case reports of anaphylaxis to polyhexanide. One patient experienced anaphylaxis while using a wet toilet paper containing polyhexanide with the detailed history revealing 3 episodes of anaphylaxis during wound care with polyhexanide [4], two patients suffered perioperative anaphylaxis to polyhexanide [5, 6]. Our case report is thus the second to describe a patient who experienced anaphylaxis to polyhexanide during wound care.

Case Report

A 77-year-old female patient presented to our day care clinic for wound treatment of her leg ulcer for the third time. She had concomitant varicose veins and stasis dermatitis. Relevant comorbidities comprised arterial hypertension, peripheral arterial disease and polyneuropathy. She reported known allergies towards amoxicillin and ciprofloxacin presenting with type I hypersensitivity reaction as well as an allergy towards cefuroxime without any detailed history. Present medications were as follows: apixaban, ramipril, metoprolol, torasemide, spironolactone, simvastatin, gabapentin, magnesium, macrogol, tilidine and metamizole.

Skin findings showed an extensive ulcer on the left leg, clear secretion and no surrounding erythema.

Antiseptic debridement was performed using octenidine dihydrochloride and polyhexanide-based disinfectant solutions. Octenidine dihydrochloride was used for the first time and caused burning sensations so that the debridement was continued with polyhexanide only as before. During the procedure the patient suddenly developed progressive swelling of the lips and tongue, erythema and itching of the integument, dyspnea and a drop of blood pressure to 62/40 mm Hg, correspondent to grade III anaphylaxis.

Concordant with the guidelines the patient received 0.5 mg intramuscular epinephrine, a cumulative dose of 1,000 mg of intravenous prednisolone and 2 mL of clemastine [7]. She received prompt intravenous fluid replacement and oxygen supplementation via a mask. Circulation was finally stabilized with additional intravenous epinephrine. The patient was referred to the intensive care unit, and the medical staff was advised to solely use physiologic sodium chloride solution and hydrogen peroxide for wound management and to prevent latex exposure. The pain medication (metamizole and tilidine) was substituted since both substances had been administered 2 h prior to the anaphylactic reaction.

Serum tryptase was analyzed 2 h after the anaphylactic reaction. It was elevated to 11.2 g/L from basal values of 3.77 and

5.48 g/L which were measured 3 and 5 days later. Total IgE was 104 kU/L and specific IgE (inhalation allergens screen sx1, food allergens screen fx5, chemicals pax5, disinfectants pax6, ethylene oxide, formaldehyde, latex, penicillin G, penicillin V, ampicillin, amoxicillin, cefaclor) were negative. However, specific IgE to chlorhexidine was elevated to 0.45 kU/L (CAP class I). Four days later dermal provocation tests were performed. Patch test with the DKG patch test disinfection series (povidone iodine, glutaraldehyde, glyoxal trimer, chlorhexidine gluconate and benzalkonium chloride) was negative after 20 min and 24 h. A fractionated patch test with octenidine dihydrochloride and polyhexanide in a dilution series of 1:1,000, 1:100, 1:10, and pure showed minimal erythema to pure octenidine dihydrochloride after 15 min. Skin prick and patch tests with pain killers were negative.

The optimal time frame for dermal provocation is 4–6 weeks after the allergic reaction to decrease the false-negative rate. In a case series of 2 patients with anaphylaxis to chlorhexidine, no sensitization was found in the skin prick test in the first week after the reaction while it was positive in both cases 6 weeks later [8]. Skin tests were repeated about 6 months later, starting with a rub test. There was no reaction to chlorhexidine gluconate, polyhexanide, atovaquone/proguanil, or octenidine dihydrochloride. The skin prick test, however, showed a slightly positive reaction to polyhexanide after 20 min (wheal diameter 3 mm). The wheal diameter increased to a maximum of 7 mm within 90 min. As before there was no reaction to chlorhexidine.

This finding encouraged further laboratory tests. A basophil activation test with chlorhexidine and polyhexanide was performed with basophils of the patient and 2 controls. There was no activation upon stimulation with chlorhexidine. However, with polyhexanide the basophil activation test was positive with a maximal activation of 15.17% of the cells at a 0.1 µg/mL concentration. The negative control was reliable, but the patient did not react to the positive control (1 mg/mL of a monoclonal anti-human IgE antibody; clone BE5; EuroBioSciences, Friesoythe, Germany), assigning her to the 5–10% of nonresponders [9]. Nevertheless, since there was a marked activation of basophils upon stimulation with polyhexanide but not of the basophils of the 2 control patients the positive result was assessed to be likely specific.

In a next step, we further evaluated this result by inhibition studies (Fig. 1). Varying concentrations of polyhexanide and chlorhexidine (0.1–100 µg/mL in a total volume of 20 µL) were added to 180 µL of the patient serum to assess cross-reactivity. The concentration of chlorhexidine-specific IgE was already low initially (0.36 kU/L). However, the binding of specific IgE to chlorhexidine to a solid phase was further inhibited by 33% to a maximum of 0.24 kU/L by addition of chlorhexidine (100 µg/mL). Strikingly, addition of polyhexanide (100 µg/mL) resulted in a stronger maximal inhibition of 67% to 0.12 kU/L. The lowest concentration of polyhexanide (0.1 µg/mL) yielded an inhibition of 31% to 0.25 kU/L. Results suggest a cross-reaction between chlorhexidine and polyhexanide. Finally, the sensitization was substantiated by elevated specific IgE to polyhexanide of 2.9 kU/L. The polyhexanide ImmunoCAP was not commercially available and kindly provided by ThermoFischer Scientific, Phadia AB, Uppsala, Sweden.

We diagnosed grade III anaphylaxis to a polyhexanide-based disinfectant. The patient gave her written informed consent to the publication of pictures and data.

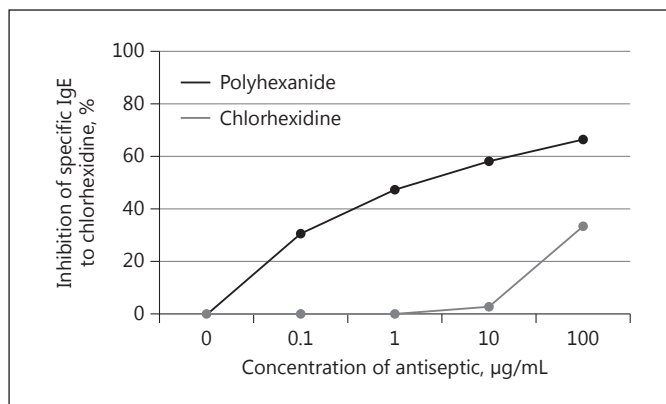


Fig. 1. Inhibition of specific IgE binding to chlorhexidine by polyhexanide and chlorhexidine. Varying concentrations of polyhexanide and chlorhexidine (0.1–100 µg/mL) were added to the patient serum to assess cross-reactivity. The concentration of chlorhexidine-specific IgE was already low initially (0.36 kU/L). However, the binding of specific IgE to chlorhexidine to a solid phase was further inhibited by 33% to a maximum of 0.24 kU/L by addition of chlorhexidine (100 µg/mL). Strikingly, addition of polyhexanide (100 µg/mL) resulted in a stronger maximal inhibition of 67% to 0.12 kU/L. The lowest concentration of polyhexanide (0.1 µg/mL) already yielded an inhibition of 31% to 0.25 kU/L. Results suggest a cross-reaction between chlorhexidine and polyhexanide. The highly sensitive test (Phadia Thermo Fisher) applied in these measurements allows for a test negativity cutoff of 0.1 kU/L.

Discussion

Our patient suffered from anaphylaxis due to polyhexanide after the substance had repeatedly been used for wound treatment in the past without causing any symptoms. Results from specific IgE testing and inhibition studies suggest rather cross-reactivity between chlorhexidine and polyhexanide than cosensitization in our patient. Chlorhexidine and polyhexanide share the hexamethylene biguanide structure motive, accounting for a presumed cross-reactivity (Fig. 2). In addition, chlorhexidine contains a 4-chlorophenyl aromatic ring. Since chlorhexidine is widely used in wound care and in everyday cosmetic products, a former exposure of our patient seems likely even though no use of chlorhexidine in the patient's wound care was documented. Reasoning from the more prominently elevated specific IgE to polyhexanide of 2.9 kU/L compared to 0.45 kU/L chlorhexidine-specific IgE, the basophil activation upon stimulation with polyhexanide and results from inhibition studies we presume a primary sensitization against polyhexanide and a cross-reactivity to chlorhexidine. Likewise, in vitro cross-reactivity between both antiseptics was postulated following inhibition assays

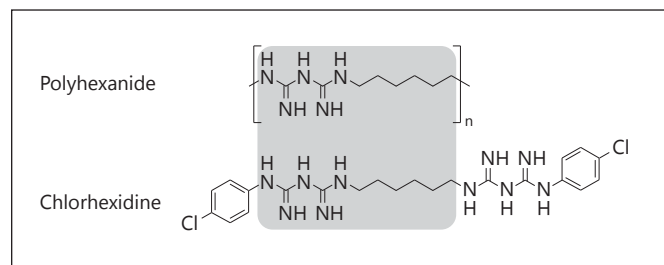


Fig. 2. Comparison of polyhexanide and chlorhexidine structural formulas. Chlorhexidine and polyhexanide share the hexamethylene biguanide structure motive (highlighted in gray color), accounting for a presumed cross-reactivity. In addition, chlorhexidine contains a 4-chlorophenyl aromatic ring.

of sIgE binding to experimental polyhexanide ImmunoCAP in the case report of anaphylaxis to polyhexanide described by Kautz et al. [4]. In both cases, inhibition studies display a higher avidity of the patients' sIgE to polyhexanide and Kautz et al. further argue for a genuine polyhexanide sensitization by indicating that sIgE to polyhexanide were tested negative in 3 patients with chlorhexidine allergy. Our case shows that sensitization might occur at any time, and cross-reaction (or cosensitization) is possible within the group of biguanides. Many patients with anaphylaxis to chlorhexidine had a mild local reaction before [10]. It remains to be seen whether local reactions to polyhexanide might be indicative for potential anaphylaxis in the future and serve as a risk marker. Individuals who are frequently exposed to polyhexanide like patients with chronic leg ulcers or frequent surgical procedures and medical staff might suffer from an increased risk to develop sensitization. Since polyhexanide is not only used in medical products, but also in cosmetics, it is important to be alert in this regard for both patients and physicians. While cross-reactivity between polyhexanide and chlorhexidine might be a diagnostic pitfall in identifying the causative allergen, the clinical relevance of in vitro cross-reactivity has not yet been established for these disinfectants. Given that chlorhexidine allergy is rather common, anaphylaxis to polyhexanide has only been reported scarcely and Kautz et al. [4] did not detect IgE reactivity to polyhexanide in 3 patients with chlorhexidine allergy, the clinical relevance of cross-reactivity might be overrated. However, caution with regard to a possible cross-reactivity must prevail whenever either allergy is suspected. Polyhexanide should be considered as a possibly emerging allergen and be replaced by antiseptics that are structurally different from biguanides where necessary.

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Author Contributions

J.A.S.: conception and design of case study, analysis and interpretation of the data, drafting of the article, final approval of the version to be published. B.S.: acquisition of data, analysis and interpretation of data, critical revision of the article for intellectual content, final approval of the version to be published. R.B.: conception and design of case study, analysis and interpretation of the data, critical revision of the article for intellectual content, final approval of the version to be published.

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