

CASE REPORT

Anaphylaxis after disinfection with 2% chlorhexidine wand applicator

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SUMMARY

A 54-year-old man with end-stage renal failure attended for dialysis. Within seconds of applying 2% w/v chlorhexidine (ChloraPrep 3 mL Wand Applicator) to the skin surrounding the insertion point of his dialysis catheter (Tesio catheter), he developed pruritus, urticaria, shortness of breath, hypotension and reduced responsiveness. Treatment for anaphylaxis was initiated with rapid improvement of his symptoms, and he made a full recovery. Allergy to chlorhexidine was confirmed with skin testing, and the patient was warned against all future exposure to chlorhexidine. Subsequent dialysis without chlorhexidine was uneventful.

BACKGROUND

Chlorhexidine is a non-prescribed antiseptic agent widely used in the healthcare setting, and in recent years increasing concentrations have been brought into use. Chlorhexidine is a bisbiguanide and has bactericidal and fungicidal activities against a range of potential pathogens.¹ Adverse reactions to chlorhexidine include contact dermatitis (type IV delayed hypersensitivity) and IgE-mediated allergy (type I hypersensitivity) ranging from urticaria to anaphylaxis and cardiac arrest. Anaphylaxis may not readily be attributed to chlorhexidine especially when the exposure occurs through chlorhexidine-impregnated antiseptic swabs, dressings or coatings of medical devices. Increased awareness about the use of chlorhexidine in these types of devices should alert doctors to investigate for chlorhexidine allergy in cases of anaphylaxis occurring in the healthcare setting where exposure may be widespread but hidden.

CASE PRESENTATION

We describe a 54-year-old dialysis patient, who attended for his regular dialysis session in the late afternoon. He had been well all day and had taken his regular medication including chlorphenamine 4 mg for a chronic itch. He had not been eating anything unusual and had an egg mayonnaise sandwich approximately 3 hours prior to arriving at hospital. Prior to the procedure, the dressing covering his Tesio catheter was removed by the dialysis nurse, and the area around the insertion point on the chest was scrubbed with a ChloraPrep 3 mL Wand Applicator. Within seconds, the patient experienced widespread intense itchiness, and an urticarial rash developed. He then developed shortness of breath and dizziness before becoming

less responsive. The emergency medical team was called. His blood pressure had dropped to 70/40, and his heart rate was 70 (it was noted that the patient was on beta-blockers). His oxygen saturation decreased to 92%.

Treatment for anaphylaxis was initiated with intramuscular epinephrine 200 µg followed by intravenous hydrocortisone 200 mg and chlorphenamine 10 mg. High flow oxygen, nebulised epinephrine 500 µg and a 750 mL fluid bolus were also administered. His symptoms settled during the next 15 min. His blood pressure increased to 110/76, and his rash improved. After the patient was stabilised, he was observed closely until the next morning. He was presumed to be allergic to chlorhexidine, and the immunology team were asked to provide further management. It is noteworthy that previous repeated exposure to the same chlorhexidine product had not elicited any reaction, not even local skin irritation or hives.

In addition to end-stage renal failure, the patient had a medical history of ischaemic heart disease, diabetes, high cholesterol, peripheral vascular disease and a left below-knee amputation in 2011. His regular medications included amlodipine 10 mg once daily, aspirin 75 mg once daily, bisoprolol 1.25 mg once daily, folic acid 5 mg once daily, ramipril 2.5 mg once daily, sertraline 100 mg once daily, lansoprazole 30 mg once daily, chlorphenamine 4 mg once daily and ticagrelor 90 mg twice daily. He had no known drug allergies. The patient was an ex-smoker and did not drink alcohol.

INVESTIGATIONS

The tryptase level 1 hour after the reaction was 31.5 µg/L. This dropped to 21.1 µg/L 12 hours later. Tryptase levels 4 days, 1 month and 6 months later were 16.2, 13.2 and 16.8 µg/L (Normal Range (NR) <11.4 µg/L), respectively. Serial chlorhexidine IgE levels were 0.16, 0.20, 0.14 and 0.04 kAU/L at 4 days, 1 month, 6 weeks and 6 months, respectively (NR <0.35 kAU/L).

Skin prick testing to 0.5% chlorhexidine revealed a 10 mm wheal, and positive and negative controls showed appropriate responses (8 and 0 mm, respectively). Intradermal testing to 0.0002% chlorhexidine was positive with a wheal diameter increasing from 6 to 15 mm. Both tests used validated concentrations.²

DIFFERENTIAL DIAGNOSIS

The typical clinical presentation and increased tryptase level after the reaction supported the



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diagnosis of anaphylaxis. Chlorhexidine was identified as the culprit by positive skin prick tests and intradermal tests, in addition to the high index of suspicion from the history.

OUTCOME AND FOLLOW-UP

We advised complete avoidance of chlorhexidine-containing products in the home including disinfectants and cleaning solutions, mouthwashes, dressings, toothpaste, creams and lozenges. In addition, he was advised to disclose his allergy on any contact with the health service to avoid accidental re-exposure.

The patient was provided with an epinephrine autoinjector, instructed on its use in an emergency and advised to wear a Medic Alert bracelet indicating his diagnosis.

DISCUSSION

Anaphylactic reactions to chlorhexidine are rare, and their true incidence is unknown. Odedra and Farooque found 65 case reports of chlorhexidine anaphylaxis published between 1994 and 2013.³ We reviewed six epidemiological studies of anaphylaxis where a detailed breakdown of drug causes was given; from a total of 1185 cases, none were attributed to chlorhexidine.^{4–9} However, in centres routinely testing for chlorhexidine as part of investigations for anaesthesia-associated allergies, chlorhexidine allergy is relatively common, with a reported prevalence of 9.6% in Denmark,¹⁰ 5.2% in Belgium¹¹ and 8.7% and 5% at two centres in the UK.^{12 13}

Cases of chlorhexidine anaphylaxis described in the literature often occur during surgery and may involve multiple routes of exposure.^{3 14 15} For example, during one surgical procedure, a patient may be exposed to chlorhexidine-impregnated catheters, a chlorhexidine-containing urethral gel and topical chlorhexidine skin disinfection prior to cannula insertion, regional anaesthesia and surgical incision sites.

Some reactions result from the oral application of chlorhexidine, with the most severe involving dental procedures where a degree of contact with the bloodstream has probably occurred. Two cases of death following anaphylaxis have been reported in patients who used a chlorhexidine mouthwash to irrigate a tooth socket following extraction.¹⁶

In other cases, such as the one reported here, chlorhexidine is applied to the skin. In most instances, the source of systemic absorption is an area of skin barrier compromise such as a burn,¹⁷ a wound¹⁸ or dermatitis.¹⁹

We found no similar reports in the literature of anaphylaxis soon after a single application of a ChlorPrep 3 mL Applicator. Allergic reactions to chlorhexidine are often preceded by milder reactions such as localised or generalised urticaria.^{15 20} Such incidents could not be identified in this patient but may have been overlooked, or otherwise symptoms may have been masked by his daily treatment with antihistamines.

It is not clear why the allergy developed after years of non-symptomatic exposure to chlorhexidine. However, inflamed skin is increasingly being implicated as a route of sensitisation. This is supported by animal models^{21–23} and the likely causal link between atopic dermatitis preceding the development of food allergy.²⁴ Perhaps chlorhexidine applied to inflamed skin penetrated the damaged stratum corneum. In the presence of danger signals and inflammatory cytokines,²⁵ resident antigen-presenting cells become activated and may process haptenised chlorhexidine.²⁶ This would lead to recruitment of lymphocytes through interaction between major histocompatibility complex molecules and T cell receptors. In the presence of type 2 cytokines, B cells can class switch to produce chlorhexidine-specific

IgE. During subsequent exposure to the allergen, IgE on the surface of mast cells is cross-linked, leading to degranulation and the release of histamine and other mediators of allergy. In this patient, the mechanism is most likely to be IgE mediated, based on the clinical history and convincing skin test results despite the fact that the specific IgE was not elevated.

A significant increase in the serum tryptase level was seen soon after the reaction, decreasing at 12 hours and at 4 days. The baseline level was noted to be slightly elevated, which was confirmed on measurements 1 and 6 months later. It has been described previously that patients on dialysis have slightly elevated baseline levels of serum tryptase. In a study of 188 patients, Sirvent *et al*²⁷ showed that the average tryptase levels were higher in patients on dialysis (14.89 µg/L) compared with those with an estimated glomerular filtration rate ≥ 60 mL/min (6.72 µg/L), $p < 0.01$. Tryptase is a 134 kDa molecule and, therefore, reduced renal elimination due to renal impairment is unlikely to be the explanation. The authors hypothesised that this finding may be a consequence of the proinflammatory state of patients with renal failure.

In our patient, chlorhexidine was identified as the trigger for anaphylaxis by positive skin prick and intradermal tests using validated concentrations. Interestingly, his specific IgE tests remained negative on repeat testing over 6 months. A study of patients with chlorhexidine anaphylaxis showed that only 1 out of 23 had a negative specific IgE test 2–4 months after the reaction.²⁸ The reason for the negative results in our patient may be a reflection of the fact that patients with renal failure appear to have lower levels of IgE in general.²⁹

While many chlorhexidine cleaning solutions have a concentration of 0.5%, UK national guidelines recommend the use of 2% chlorhexidine single application products.³⁰ We suspect that the use of a higher concentration of chlorhexidine in the UK may be contributing to allergic sensitisation to chlorhexidine. This is suggested by the following studies of type I or type IV hypersensitivity reactions. Garvey *et al*³¹ studied 104 healthcare workers in Denmark who were exposed to 0.5% chlorhexidine hand washes and found no cases of type I or type IV reactions to chlorhexidine. Nagendran *et al*³² found IgE sensitisation to chlorhexidine in 4 symptomatic healthcare workers out of 86 questioned in a district hospital in UK, where 4% chlorhexidine (Hydrex) hand washes were used. Another study involving patch testing (for type IV hypersensitivity) of healthcare workers in Poland found that three surgeons exposed to 4% chlorhexidine were all patch test positive, compared with 8 out of 333 nurses tested.³³

The rationale for using a 2% chlorhexidine concentration is unclear. In a study comparing the effectiveness of different concentrations of topical chlorhexidine on 74 volunteers, Nishihara *et al*³⁴ found no difference between 0.5%, 1% and 2% solutions. Several studies comparing different chlorhexidine concentrations in dental applications have yielded mixed results.^{35–37} In Japan, in the 1980s, following six cases of severe anaphylaxis attributed to chlorhexidine (used in concentrations between 0.05% and 1.0%),³⁸ it was suggested that the use of chlorhexidine on mucous membranes should be avoided altogether. On wound surfaces, the lowest bactericidal concentration of 0.05% was recommended for skin disinfection.

Over the years, warnings about the risk of allergic reactions to chlorhexidine have been published from both physicians and regulatory agencies. The Food and Drug Administration (FDA) issued a warning to increase awareness about allergic reactions to chlorhexidine-impregnated central venous catheters in 1997 after they were attributed to several cases of chlorhexidine anaphylaxis.³⁹ Reporting

a case of chlorhexidine anaphylaxis after urethral catheterisation in Australia, Stewart and Lenaghan⁴⁰ suggested the use of a chlorhexidine-free lubricant gel for urological procedures. A recent FDA warning issued in February 2017 urges manufacturers of chlorhexidine gluconate-containing over-the-counter antiseptic products to include a warning on the risk of serious allergic reactions.⁴¹

Cases of chlorhexidine allergy are increasingly identified in the UK,¹² some with severe reactions and a few with fatal outcomes.¹⁶ While chlorhexidine is probably the best disinfectant available and the benefits are unquestionable, it is important to be aware of its allergenic potential, and use chlorhexidine only when necessary. We suggest that UK national guidelines for preventing healthcare-associated infections be reviewed again with a view to updating the evidence base and ensuring that only minimum effective concentrations of chlorhexidine are recommended.

Learning points

- ▶ Chlorhexidine has the potential to trigger anaphylaxis in patients who become sensitised after repeated exposure.
- ▶ Mild reactions such as localised or generalised urticaria may precede more serious reactions.
- ▶ Chlorhexidine anaphylaxis may be triggered via several different routes of exposure—including contact with skin wounds, oral mucosa, urethral gels and indwelling catheters.
- ▶ The use of higher concentrations of chlorhexidine may increase risk of sensitisation.

Contributors All authors contributed to the article. SB wrote the majority of the article including the background, the case presentation, part of the discussion and the learning points sections. He carried out the allergy testing on the patient. He was also involved in the treatment and follow-up of the patient. SS wrote part of the discussion section and the learning points section. She carried out some of the literature search. LHG reviewed the article and suggested changes and improvements. She wrote sections of the discussion. VN was involved in writing the summary, the case presentation, the differential diagnosis, the outcome and follow-up and the discussion sections. She edited the whole article. She also took part in the allergy testing of the patient and was the consultant in charge of the patient's allergy care.

Competing interests None declared.

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