

Anaphylaxis related to disinfection with chlorhexidine in a teenager treated for cancer

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Abstract

Introduction: Literature shows upcoming allergy to chlorhexidine due to the widespread use of the disinfectant within and outside surgical settings. Only a few case reports have been published regarding the use of topical chlorhexidine disinfectant outside surgery and only a minority of these within the pediatric population.

Case report: We present a case-report of a teenager, treated for acute lymphoblastic leukemia who developed an anaphylactic shock after repeated chlorhexidine use for skin disinfection at the insertion of a central venous catheter during his chemotherapy treatment. Preceding minor symptoms such as local swelling and pruritus were not recognized as possible allergy to chlorhexidine.

Management and outcome: He was treated with two doses of intramuscular adrenaline and transferred to the pediatric intensive care unit where he fully recovered. Specific IgE testing was positive for chlorhexidine. A total avoidance of chlorhexidine was instructed.

Discussion: A similar case was published regarding an anaphylaxis after use of chlorhexidine disinfectant for a dialysis catheter. Almost all other case reports of anaphylactic shock were found within surgical settings or after insertion of an impregnated central venous catheter/urine catheter. We suggest that some of the disinfectant might have been flushed in the catheter and then caused an anaphylactic reaction. The link between symptoms and chlorhexidine was not made until an anaphylactic reaction occurred. Literature data show that chlorhexidine often causes mild preceding symptoms before an anaphylaxis occurs. So let awareness arise around this 'hidden allergen' of which warning reactions often are being missed.

Keywords

Chlorhexidine allergy, topical use, pediatric

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Background

Chlorhexidine diacetate is a bisbiguanide antiseptic with broad spectrum bactericidal (Gram positive and Gram negative bacteria including *Staphylococcus aureus*) and fungicidal activities. It has been increasingly used over the past two decades, not only for local disinfection and impregnation of medical devices but also in antiseptic mouthwashes, dental gels, lens solutions and cosmetics.^{1,2}

Adverse reactions to chlorhexidine have been frequently reported, especially when using impregnated central venous catheters and urine catheters.³ To our knowledge, only one case report has been published

regarding an anaphylaxis due to the use of chlorhexidine for local disinfection of a dialysis catheter in an adult,⁴ and there are only very few cases reporting

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allergic reactions to topical use of chlorhexidine prior to or during surgery.^{1,5-11} A literature search was performed using Pubmed database with following mesh words: chlorhexidine, anaphylaxis (allergy, anaphylactic), children (child), topical. We describe a case of anaphylaxis in a 16-year-old boy after repeated use of chlorhexidine for local disinfection of insertion of a central venous catheter and have summarized the available literature data.

Case presentation

A male teenager of 16 year old was diagnosed with a T-cell acute lymphoblastic leukemia for which he was treated according to the EORTC 58081 protocol during four months (https://www.eortc.org/research_field/clinical-detail/58081/). He had a negative personal and family history of allergies. He had developed a temporary diabetes and hypertension due to high-dose cortisone use which was treated with subcutaneous insulin injections for one month and oral amlodipine for two months. His concurrent medication, apart from chemotherapy was ranitidine and co-trimoxazol. As per local policy, skin disinfection of the insertion site of the catheter is performed with a chlorhexidine 2% in alcohol solution before every manipulation of the central venous catheter.

After three weeks of treatment, he received a plasma transfusion because of hypofibrinogenemia due to treatment with asparaginase. During this transfusion, he developed urticaria for which he was treated with intravenous hydro-cortisone and clemastin (an antihistaminic). Subsequent plasma transfusions with prophylactic intravenous clemastin were completed without any obvious allergic reactions.

After a few weeks, the patient experienced urticaria and swelling of the face without difficulties of breathing or change in vital signs, during flushing of his central venous catheter after a plasma transfusion. Again, after treatment with intravenous hydro-cortisone, all symptoms disappeared. This reaction was again interpreted as an allergy reaction to plasma transfusion.

Two weeks later, he experienced a similar reaction of facial urticaria with pruritus without change in vital signs, during flushing (with physiological saline) of the central venous catheter before any medication or blood product had been administered.

At this time, rescue medication was not necessary as symptoms were mild and disappeared spontaneously after 10 min.

Three weeks later, a reaction of the same type appeared without escalation of symptoms and again with spontaneous resolution. No investigations were executed yet at this time, as there were multiple procedures of flushing the central catheter without

any problem. Moreover, the reactions that occurred could not be linked to one specific type of medication.

Three months after his first reaction, the patient developed a severe allergic reaction with anaphylactic shock after disinfection of the skin at the insertion site of the central catheter with a chlorhexidine 2% solution and flushing of the catheter with physiological saline before administration of any medication. He started vomiting and had abdominal cramps, sudden hypotension with loss of consciousness and bradycardia without respiratory symptoms. After administration of a fluid bolus, intravenous hydro-cortisone, clemastin and a first dose of intramuscular adrenaline (500 mcg), he still suffered from hypotension and decreased consciousness. A second dose of intramuscular adrenaline and intravenous fluid bolus was administered after which his parameters slowly recuperated. He was referred to the pediatric intensive care unit for further care and investigations.

Tryptase, measured 6 h after the event was 7.27 µg/l and clearly elevated as compared to baseline tryptase one month after the event 2.42 µg/l, which is suggestive for mast cell activation and anaphylaxis.

A chlorhexidine allergy was suspected and confirmed because a blood exam showed elevated specific IgE for chlorhexidine 4.77 kU/L (normal <0.1 kU/L). Total IgE was 230 kU/L (normal <100 KU/L). Skin prick testing and intradermal tests with chlorhexidine were not executed to avoid anaphylaxis during the skin tests and because the specific IgE for chlorhexidine was elevated and this case clinically suggested chlorhexidine allergy.

Latex allergy was ruled out since skin prick test with latex extract was negative. Latex is still being used without new reactions occurring.

Other causes for this shock-syndrome like embolism, thrombi, cardiac arrhythmias were excluded through laboratory investigations, cardiac echography, duplex echography of the upper limbs, angio-CT scan of the thorax and intensive monitoring.

Instructions for total avoidance of chlorhexidine and how to manage future reactions were given to the patient. Allergy alerts were noted in his medical file. An Epipen® (300 µg epinephrine) was prescribed for ambulatory use.

Discussion

The true incidence of chlorhexidine allergy is unknown. Literature data describe only a few case reports and case series about anaphylactic reactions to chlorhexidine with incidences ranging from 5 to 10%.^{4,12}

In 1984, the first anaphylaxis due to chlorhexidine was described. Beaudouin et al.¹³ described a series of

50 case reports of chlorhexidine anaphylactic shock between 1994 and 2004. Odedra and Farooque² reported another 15 case reports till 2013 of which almost all of them occurred within surgical setting or after insertion of an impregnated central venous catheter/urine catheter. Another research done by Weng et al.¹⁴ described 14 case reports of anaphylactic shock after insertion of a coated central venous catheter between 1997 and 2014. According to Odedra and Farooque before 2013, only one case report was published regarding an anaphylactic shock syndrome outside surgical setting or insertion of a chlorhexidine-coated catheter, namely while using chlorhexidine containing jelly during rectal examination.^{2,15} Our research confirms that up till 2013, almost all case reports of anaphylactic shock due to the use of chlorhexidine are found within surgical setting or after the insertion of a chlorhexidine impregnated catheter. On the contrary, Egner et al.⁸ describe in a multicenter study in the UK 104 cases of possible anaphylactic reaction to chlorhexidine within surgical setting between 2009 and 2013. This is quite a high number not being described elsewhere, although assumptions are being made the actual prevalence of chlorhexidine allergy is underestimated.

Between 2013 and 2018, case reports regarding allergic reactions after use of chlorhexidine keep being published.^{1,4,8–11,14,16,17} Most of the reactions occur within surgical setting or after insertion of a coated central venous catheter or urine catheter,^{1,9,10,14} some of the reactions occur after the use of Instillagel® when being brought in contact with the patients mucosa,^{1,16} others after use of antiseptic mouthwash.^{8,17}

Our case describes an anaphylactic reaction after topical use of chlorhexidine for disinfection of the skin at the insertion site of a central venous catheter in a non-operative setting. Bahal et al. published a similar case regarding an anaphylaxis after use of chlorhexidine disinfectant for a dialysis catheter. This routine dialysis patient underwent an anaphylactic shock with need of intramuscular epinephrine after disinfection of his catheter with topical chlorhexidine disinfectant. Tryptase levels, skin prick testing and intradermal testing all suggested a chlorhexidine allergy without ever showing previous symptoms to the same disinfectant.⁴

Several times, our patient suffered from mild allergic reactions with urticaria in the face, pruritus and sometimes swelling of the lip which disappeared spontaneously within 10 min. The link between symptoms and chlorhexidine was not made until an anaphylactic reaction occurred. Literature data show that chlorhexidine often causes mild preceding symptoms before an anaphylaxis occurs. These warning reactions are often being missed.^{2,4,11,16,18} Our case demonstrates how

easily these warning symptoms can be missed or misinterpreted.

Based on these data, we suggest that some of the disinfectant might have been flushed in the catheter and then caused an anaphylactic reaction as symptoms were initiated immediately after flushing of the catheter. The reason why the patient did not suffer from allergic symptoms each time the catheter was flushed possibly lies in the fact that a different technique of disinfecting and flushing of the catheter might be used, depending on the routine of the nurse. Also the process of sensitization to chlorhexidine can be a possible explanation. Bahal et al. explain in their case report that an inflamed skin can be a route of sensitization as cytokines are already present in the damaged stratum corneum. This process can lead to the direct production of chlorhexidine specific IgE through B-lymphocytes and it can prime mastcells. With repeated exposure to chlorhexidine, mastcells are quickly activated leading to the release of histamine and other mediators of allergy.^{4,11} In our case however, there was no knowledge about inflamed or damaged skin, although there was some scar tissue present at the insertion site of the catheter.

Analyzing this case, the Naranja Algorithm Assessment Score¹⁹ is 6 concluding a probable adverse drug reaction. We cannot speak of a definite adverse drug reaction because the drugs were not re-administered after the anaphylaxis occurred and no toxic dose was found in blood samples (Table 1).

From literature, it is known that most patients with an anaphylactic reaction to chlorhexidine suffer from severe hypotension, though most of them are under general anesthesia and other symptoms cannot be expressed by the patient. Respiratory symptoms tend to be less frequent.^{2,4,8,14} This was also the case in our patient, where he suffered from severe hypotension with loss of consciousness but without any respiratory symptoms.

Most patients have no history of atopy and there is a preference for males.^{2,8,10}

Two deaths have been reported after the use of chlorhexidine mouthwash after dental extraction. No other fatal cases have been reported so far,^{14,20} though often refractory shock is noted with need of multiple doses of epinephrine.^{2,4,9} Also in our case, the patient needed a second dose of epinephrine before vital parameters recovered.

Tryptase testing can be useful to differ allergic reaction from systemic mastocytosis, but must be executed at the right timing, namely within 1 h, 4 h and 24 h after the event and a decrease must be seen.² A mast cell activation is very likely if tryptase measurement at the acute moment is higher than baseline level,

Table 1. Adverse drug reaction probability scale: the Naranjo algorithm.

Naranjo algorithm	
1. Are there previous conclusive reports on this reaction?	Yes (+1)
2. Did adverse event appear after the suspected drug was given?	Yes (+2)
3. Did the adverse reaction improve when the drug was discontinued or a specific antagonist was given?	Yes (+1)
4. Did the adverse reaction appear when the drug was readministered?	Do not know or not done (0)
5. Are there alternative causes that could have caused the reaction?	Yes (-1)
6. Did the reaction reappear when a placebo was given?	No (1)
7. Was the drug detected in any body fluid in toxic concentrations?	No (0)
8. Was the reaction more severe when the dose was increased, or less severe when the dose was decreased?	Do not know or not done (0)
9. Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	Yes (+1)
10 Was the adverse event confirmed by any objective evidence?	Yes (+1)
→ Naranjo score	6
→ Adverse drug reaction	PROBABLE
Cut-off points include:	
≤0 DOUBTFUL ADR	
1–4 POSSIBLE ADR	
5–8 PROBABLE ADR	
≥9 DEFINITE ADR	

namely 1.2 times baseline plus two, as confirmed in our case.²¹

There is no evidence that chlorhexidine allergy can resolve over time. Life-time avoidance is indicated. There is no evidence for the use of immunotherapy.² Questions rise regarding the effectiveness and cost-benefits of chlorhexidine as a topical antiseptic and impregnator of catheters taking into regard the growing allergy prevalence.²

Conclusion

Literature shows that the incidence of chlorhexidine allergy with severe anaphylaxis is increasing since the start of its use 60 years ago. As it is used in many different medical interventions (surgery, disinfection, impregnation of catheters), it is important for clinicians to be aware of the possibility of a severe adverse reaction. Symptoms of anaphylactic shock after exposure to chlorhexidine are often recognized too late with delay of correct treatment. Secondly, it is important to look for chlorhexidine alternatives for disinfection/impregnation, as in the future allergy to chlorhexidine can become more and more prevalent.

Chlorhexidine allergy often starts with minor symptoms, but can evolve to an anaphylactic shock syndrome. Therefore, chlorhexidine is known as 'the hidden allergen'. It is important to think of chlorhexidine allergy and test it early in the process during minor

symptoms so anaphylaxis can be prevented. Still too often these warning reactions are being missed.

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