

Chlorhexidine wipes: Time to stop and think about allergy

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Summary

We report three precautionary cases of perioperative anaphylaxis to chlorhexidine isopropyl alcohol antiseptic wipes (CAW). In two cases, the patients were inadvertently re-exposed to CAW despite known chlorhexidine hypersensitivity. Chlorhexidine has been described as ‘the hidden allergen’. As a result, patients may suffer multiple reactions before chlorhexidine is confirmed as the cause. Healthcare workers may not recognize that products they use for common clinical steps contain chlorhexidine. These cases highlight the need for constant vigilance to facilitate the safe management of patients with a history of chlorhexidine anaphylaxis.

Keywords

allergen, anaphylaxis, allergen, chlorhexidine, disinfectants, drug hypersensitivity

Introduction

After muscle relaxants and antibiotics, chlorhexidine is the third most common cause of perioperative anaphylaxis in Australia, New Zealand and the United Kingdom.^{1,2} Chlorhexidine accounted for almost 10% of perioperative anaphylaxis in the recently released National Audit Project 6 (NAP6) report from the United Kingdom.² Multiple routes of exposure were identified in the majority of cases including skin preparation, coated central venous catheters and urethral gels. The widespread clinical use of chlorhexidine as a component of everyday clinical tools has led to its status as a hidden allergen, chlorhexidine isopropyl alcohol antiseptic wipes (CAWs) being a prime example.³ These wipes have superseded plain alcohol wipes (PAWs) for many antiseptic applications and are the default preparation used in many hospitals throughout Australia prior to peripheral intravenous cannulation (PIVC).⁴ However, it appears that it is not widely recognized that CAWs can cause anaphylaxis. Here, we present three cases of proven anaphylaxis to CAWs. The implications for clinical practice are discussed. Written consent for publication was obtained for each case.

Case 1

A 52-year-old male presented for rhinoplasty and polypectomy. He had undergone multiple surgeries in the

past. History identified an adverse reaction discovered after removal of a plaster placed for ulnar fixation surgery. The underlying skin was noted to be red and blistered. The surgeon questioned flucloxacillin allergy at the time, but the patient also recalls being told he should avoid chlorhexidine. A note of ‘antiseptic wash allergy’ was added to his medical record and no further testing was performed. The patient had no other history of atopy. The operative team for his nasal surgery planned to avoid exposure to chlorhexidine and flucloxacillin.

His intraoperative course was unremarkable. PIVC was performed with a PAW. Agents utilized for general anaesthesia (GA) included midazolam, fentanyl, propofol, rocuronium, sevoflurane, dexamethasone, parecoxib, cefalotin, metoclopramide, tropisetron, paracetamol, neostigmine, glycopyrrolate and metoprolol. The patient reported pain 30 min after arrival in the recovery unit and intravenous (IV) morphine 2mg was administered. Within minutes he became agitated with severe pruritis and subcostal pain,

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followed by reduced consciousness. The resuscitation team noted bradycardia of 30 bpm, hypotension (65/40 mmHg) and reduced oxygen saturation to 88%. Two boluses of 50 µg IV adrenaline and 2 L of normal saline were administered. The patient stabilized and was transferred to intensive care with an uneventful recovery thereafter. The first serum tryptase was taken 6 hours after the reaction occurred and was elevated at 15.9 µg/L (normal < 13 µg/L) and had fallen to 7 µg/L at 12 hours. The referral for further testing postulated a diagnosis of anaphylaxis to morphine.

Intradermal skin testing (IDT) was conducted six weeks post reaction using the Fisher protocol.⁵ All agents utilized for GA including cefalotin and morphine were tested, with negative results. Specific immunoglobulin E (sIgE) for latex was negative, <0.01 kU/L. Chlorhexidine sIgE was not performed as the test was not readily available at the time in local laboratories. IDT aqueous chlorhexidine 2% 1:100,000 was positive (11 × 10 mm wheal). Skin prick testing (SPT) aqueous chlorhexidine 0.05% also produced a positive test result (13 × 9 mm wheal).

In view of these results, the recovery nurse involved with the patient's care was contacted. Chlorhexidine allergy had been noted on handover. On recounting the steps taken prior to injection, it was confirmed that the injection port on the IV tubing was prepared with an antiseptic wipe prior to morphine administration. When asked to retrieve an antiseptic swab from the recovery store, the nurse confirmed that the wipe used had contained chlorhexidine. The staff member commented that it was not easy to confirm the presence of chlorhexidine in the wipe as the contents were displayed in very small print.

Case 2

A 58-year-old male presented for cardiac ablation for atrial flutter. History revealed well-controlled asthma and multiple surgical procedures without adverse incident. There were no allergies identified. GA was induced with propofol and midazolam, and maintained with sevoflurane. The cardiorespiratory parameters remained stable while the procedure commenced, with application of povidone iodine to skin, local anaesthetic infiltration and cardiac catheter insertion. The anaesthetist replaced the PIVC at this point using a CAW. Mild hypotension (90 mmHg systolic) occurred soon after re-siting the PIVC and was initially thought to be related to the existing arrhythmia. Cardioversion was unsuccessful. The blood pressure fell to 60 mmHg systolic, was unresponsive to metaraminol and ephedrine boluses, and was associated with oxygen desaturation. The patient was treated with a 10 µg IV adrenaline

bolus followed by an infusion, 3 L IV crystalloid, and hydrocortisone. With restoration of circulation, the patient appeared flushed and developed angioedema. Post-operative care in the intensive care unit was unremarkable. Serum tryptases were elevated consistent with anaphylaxis: 56.9 µg/L two hours after the first symptoms, 22.3 µg/L at seven hours and 12.3 µg/L 13 hours post reaction (normal < 13 µg/L).

IDT was conducted eight weeks post reaction with negative responses to propofol, midazolam and povidone iodine. Challenge tests with 1% lignocaine and 0.5% bupivacaine were negative. sIgE for latex was negative. Similar to case 1, chlorhexidine sIgE was not yet available. IDT chlorhexidine 2% 1:100,000 was positive (9 × 14 mm wheal). SPT chlorhexidine 0.05% was also positive (14 × 10 mm wheal).

Case 3

A 49-year-old male presented for transurethral resection of bladder tumour. He had no known allergies. GA and the operative procedure were uneventful. Prior to the commencement of the procedure, 2% chlorhexidine in 70% alcohol skin preparation was used over intact skin. Urethral gel utilized during the operation did not contain chlorhexidine. The patient was stable for five hours after operation completion. The injection port on the IV tubing running Hartmann's solution was wiped with a CAW and immediately flushed with normal saline. Within minutes, the patient developed severe generalized pruritis, cough and bronchospasm. He appeared flushed and developed marked facial swelling. The patient was treated with 0.5 mg intramuscular adrenaline, 5 mg nebulized adrenaline, IV hydrocortisone, promethazine, ranitidine and dexamethasone. He was admitted to intensive care and stabilized overnight. A diagnosis of chlorhexidine anaphylaxis was postulated and chlorhexidine-free precautions instituted.

The patient required urgent surgery five days later. He had developed a vesicoenteric fistula associated with a stricture in the distal sigmoid. Management included anterior resection and bladder repair. Chlorhexidine-free precautions were adopted for the operating theatre and passage throughout the hospital.¹ The intra-operative course was uneventful. Antibiotic prophylaxis included cefazolin and metronidazole, which was continued postoperatively for mildly elevated temperature and wound erythema. The patient remained stable until the second postoperative evening, when he was moved to a bed consistent with the reduced observations required. Signs regarding his chlorhexidine-free status and the PAW stored for ready use by the bedside were not moved with the patient. In the absence of the PAW, a CAW was

retrieved from the nurse's pocket to prepare the IV port and a metronidazole infusion immediately commenced. Within minutes, generalized pruritis recurred with chest tightness, and facial and body angioedema. Following the first episode, the patient had been educated regarding the use of an adrenaline autoinjector. He self-administered the intramuscular adrenaline from the bedside drawer and called for help. On arrival, the resuscitation team noted hypotension of 65/40 mmHg, generalized erythema and widespread bronchospasm. Management included IV crystalloid bolus, 50 µg IV adrenaline, nebulized salbutamol and IV hydrocortisone, promethazine and ranitidine. Serum tryptase was acutely elevated at 47.7 µg/L one hour after the reaction commenced and 16.9 µg/L at eight hours (normal < 13 µg/L). Baseline serum tryptase taken after 24 hours was normal at 3 µg/L. sIgE for chlorhexidine was positive at 2.98 kU/L (normal < 0.35 kU/L).

Discussion

We report three cases of anaphylaxis to CAWs, which occurred from 2010 to 2012. A combination of history and positive results with both SPT and IDT established the diagnosis in cases 1 and 2. The use of SPT and IDT to diagnose chlorhexidine anaphylaxis is supported in recent Australasian⁶ and British publications.² At the time of testing cases 1 and 2, sIgE for chlorhexidine was not available locally. Skin testing was not undertaken in case 3 due to positive sIgE for chlorhexidine and the clinical history. Chlorhexidine sIgE has been reported to have a sensitivity of 100% and a specificity of 97%.^{7,8} Both episodes of anaphylaxis occurred after the IV access port was wiped with a CAW immediately prior to injection. Chlorhexidine was the only allergen administered in the hour prior to both reactions. In most cases of perioperative anaphylaxis, the exposure to chlorhexidine occurs in combination with a number of other potential allergens. Research in this situation supports SPT and IDT in combination with chlorhexidine sIgE to diagnose chlorhexidine hypersensitivity,^{2,7-11} preferably performed within six months of the anaphylactic episode.²

All patients were educated regarding chlorhexidine avoidance, and the importance of checking labels in the health environment and community including mouthwash, antiseptics, handwash and personal hygiene products. They were all advised to wear Medic-Alert devices to avoid inadvertent exposure. Recently, patient education has been simplified with the release of an online patient education brochure.¹²

This is the first reported cluster of such cases. Our review of the literature identified two other separate case reports of anaphylaxis to CAWs published in 2014¹³ and 2011.¹⁴ In the first case, chlorhexidine was

not initially suspected, but rather normal saline was postulated as the allergen.¹³ Subsequent investigation revealed that the chlorhexidine within the antiseptic wipe applied prior to IV injection caused anaphylaxis. The second case of anaphylaxis occurred after a CAW was used prior to PIVC insertion in a patient with previous anaphylaxis to chlorhexidine skin preparation.¹⁴ These cases emphasize that many healthcare workers may not recognize the presence of a potential allergen when using a CAW. These wipes are utilized for many patients during a hospital admission without associated adverse reaction. It is only by increasing awareness of the possibility of anaphylaxis to the chlorhexidine in the wipes that this rare, but potentially life-threatening, phenomenon is likely to be recognized.

Chlorhexidine is an antiseptic, disinfectant and antimicrobial widely used in healthcare and community settings. It is a broad-spectrum synthetic biguanide, with bactericidal and bacteriostatic action. Chlorhexidine is cationic in nature and adheres to skin when dry, which results in persistent antimicrobial activity with limited systemic absorption.¹⁵ Compared with isopropyl alcohol applied to skin, chlorhexidine has been shown to have prolonged residual activity, and is not inactivated by blood and body fluids. For these reasons, the two are often combined.¹⁴⁻¹⁶

Hypersensitivity reactions to chlorhexidine have been reported throughout the world. These allergy reports and inclusion of the antiseptic in a large number of products in the healthcare environment have led to the description of chlorhexidine as 'the hidden allergen'.³ It has not proven possible to definitively determine the incidence of chlorhexidine-induced anaphylaxis for multiple reasons.¹⁷ The absence of mandatory reporting and regional variations throughout the world are factors.^{15,18} Initial cases from Japan regarding chlorhexidine anaphylaxis were reported in 1967, with a ban on application to mucosal surfaces since 1984.¹⁹ The Food and Drug Administration in the US and the Australian Therapeutic Goods Administration have issued warnings regarding the potential risk of hypersensitivity reaction to products containing chlorhexidine, including impregnated central venous access devices.²⁰⁻²² Despite these government warnings, chlorhexidine may be overlooked as the cause of anaphylaxis resulting in delayed diagnosis.

Hypersensitivity reactions to chlorhexidine range from contact dermatitis and delayed hypersensitivity to severe, life-threatening anaphylaxis. The majority of chlorhexidine anaphylaxis case reports involve systemic absorption, either through mucous membranes or a compromised skin barrier.^{18,23} Anaphylaxis has rarely been reported to occur after application to intact skin.²³⁻²⁵ Many patients have repeated exposures to chlorhexidine before it is identified as the cause of

anaphylaxis.^{17,26–38} As in case 1, detailed history may reveal mild reactions, such as rash or urticaria, prior to the first episode of anaphylaxis to chlorhexidine.³²

Provision of an antiseptic in the form of a wipe allows for ease of application. Routine steps such as preparing skin prior to PIVC or wiping the needleless connector (NC) prior to IV injection are simplified. Our concern is that CAWs have replaced PAWs in many clinical settings without due consideration. The available scientific evidence does not support that the risk of chlorhexidine use is justified every time these procedures are performed.

The Centers for Disease Control and Prevention (CDC) state to prepare the skin prior to PIVC with antiseptic, with options including 70% alcohol, tincture of iodine or alcoholic chlorhexidine gluconate solution. They note that the ideal choice of antiseptic remains an unresolved issue.³⁹ A recent review by Maiwald and Chan has highlighted that the use of alcoholic chlorhexidine has not been proven to be superior to other alcohol-containing antiseptics.⁴⁰ Isopropyl alcohol is shown to have the fastest immediate antimicrobial activity, but less residual activity on skin in comparison with chlorhexidine.⁴⁰ More recent guidelines recognize the risk of exposure to chlorhexidine without proven benefit and make recommendations based upon the intended duration of PIVC access. CAWs have not been shown to confer additional benefit compared with PAWs for short-term cannulation (<24 hours).⁴¹ Accordingly, the NSW Health PIVC Guideline 2013⁴² and the Australian and New Zealand College of Anaesthetists (ANZCA) Infection Control Guidelines 2015⁴¹ recommend using PAWs prior to short-term PIVC insertion. Thus, both PAWs and CAWs should be available for considered use prior to PIVC placement.

Scientific evidence supports decontamination prior to injection via an NC or IV injection port of peripheral IV access as a justified practice. A 2015 review found that the greatest risk for contamination of the PIVC after insertion is the NC, which was found to be contaminated in 33–45% of patients with normal use.⁴³ The CDC and the Infusion Nurses Society recommend decontamination prior to NC access using friction with an appropriate antiseptic (70% alcohol, chlorhexidine, povidone iodine and iodophors).^{39,44} We contend that the ready availability of CAWs has resulted in their use as the default antiseptic for this purpose without adequate risk–benefit analysis. The longer duration of effect of chlorhexidine confers no additional benefit in this setting, since decontamination will occur prior to each injection. PAWs provide rapid decontamination without the risk of direct IV injection of chlorhexidine. Consistent with this contention, the ANZCA Infection

Control Guidelines 2015 recommend the use of 70% PAWs to decontaminate vascular access ports.⁴¹

Another consideration with the use of CAWs is the requirement that the antiseptic solution is allowed to dry prior to barrier penetration.⁴⁵ Guidelines support this practice for both PIVC and decontamination prior to injection via IV access ports or NCs. The NSW PIVC guideline recommends allowing at least one minute for the skin to air dry before insertion.⁴² This allows the cationic properties of chlorhexidine to bind strongly to the skin and reduce systemic absorption.¹⁵ We have observed in our clinical practice that waiting for the solution to dry is a frequently missed step in the busy hospital environment.

Cases 1 and 3 add to the numerous reports demonstrating the risk of repeated reactions, even where a patient is known to have a history of chlorhexidine hypersensitivity.^{14,29,36,46–48} These cases emphasize the significant risk of unintended or inadvertent exposure.¹ Constant vigilance is required to prevent accidental exposure, particularly in relation to steps that are considered to be routine, such as the wiping of an NC prior to injection. The ANZCA Chlorhexidine-Free Management Guidelines¹ emphasize that alternative measures, including PAWs, must move with the patient wherever they go in hospital. Ready availability of PAWs in the immediate environment aims to reduce the likelihood that a CAW will be used by mistake. This occurred in case 3, where the PAW did not move with the patient and the nurse used a CAW from their easy-access pocket storage. ANZCA Guideline PS60 recommends that the chlorhexidine allergy warning signs must be attached to the patient's bed, such that they will move with the patient throughout the hospital.¹

Many previous authors have asserted that clearer labelling is necessary to ensure that patients are not inadvertently exposed to chlorhexidine.^{2,33,36,46} A uniform colour and symbol of adequate size on packaging, similar to latex, has been proposed.¹ The inadvertent re-exposure in case 1 highlights the fact that CAWs have limited space for writing of adequate size to readily identify the presence of chlorhexidine. NAP6 emphasized that prominent labelling of all products containing chlorhexidine would assist staff in avoiding exposing patients with known or suspected chlorhexidine allergy.²

In presenting these three cases, we raise multiple reasons to pause and think in relation to the use of CAWs. The many favourable properties of chlorhexidine have resulted in its widespread use within the hospital environment. This practice also results in repeated exposures that predispose to sensitization and subsequent hypersensitivity reactions. It is time to carefully consider the role of CAWs in clinical practice.

We recommend that both CAWs and PAWs should be retained in all locations where PIVC insertion or use are necessary. Similar to antibiotics, chlorhexidine is a valuable tool in the clinician's armamentarium against infection, but rational use demands that chlorhexidine should be used only where benefit can be demonstrated to outweigh risk for a particular application. Furthermore, clinicians need to understand the principles and prepare for the safe management of patients who require chlorhexidine-free care.

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