17 Chlorhexidine

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Key findings

- In NAP6 chlorhexidine accounted for almost 10% of all cases, and was the third most prevalent cause of anaphylaxis.
- The estimated incidence was 0.78 per 100,000 exposures.
- One case of chlorhexidine-induced anaphylaxis was fatal.
- The diagnosis was often not recognised, with anaesthetists suspecting that chlorhexidine was the culprit in approximately a quarter of the cases where it was confirmed to be.
- These included cases where a chlorhexidine-coated central venous line was not removed during anaphylaxis. This creates a risk of continued exposure to the trigger and an increasingly severe reaction.
- Three cases were potentially avoidable by better history-taking or by heeding a relevant history.
- Anaphylaxis from chlorhexidine was often delayed, but was more rapid and severe where chlorhexidine had direct access to the circulation.
- Bronchospasm was relatively infrequent as a presenting feature in chlorhexidine anaphylaxis.
- Perioperative anaphylaxis to chlorhexidine is an important healthcare risk due to its widespread presence in the healthcare setting, and it can be fatal.
- In fatal cases of perioperative anaphylaxis, a blood sample test for specific IgE for chlorhexidine may help in establishing the diagnosis.
- Testing for chlorhexidine was frequently omitted in allergy clinics. This should be done in all cases of perioperative anaphylaxis.
- Testing for chlorhexidine sensitisation is complex because a single test may be insufficient to exclude allergy.
- In cases of chlorhexidine allergy, tests against other allergens may also be positive, suggesting that more than one sensitisation is present; so when chlorhexidine is positive on testing all other relevant exposures should still be allergy tested.

What we already know

Chlorhexidine is responsible for a significant proportion of cases of perioperative anaphylaxis. Chlorhexidine exposure during the perioperative setting may occur via topical skin disinfection, chlorhexidine-coated central venous catheters, and the use of chlorhexidine-containing lubricating gels (Parkes 2009). It may not be immediately obvious that these products contain chlorhexidine – which has been called the 'hidden allergen' (Ebo 2004).

There are geographical differences in the incidence of chlorhexidine-induced perioperative anaphylaxis. It has been reported to account for 7.7% cases in the United Kingdom (Krishna *et al.*, 2014) and 9.3% in Denmark (Opstrup 2014), but it reported to be a rare culprit in France (Mertes 2016). The cause for the variation is not clear, but may be related to under-recognition and to differences in practice (for example, more use of povidone-iodine and less use of chlorhexidine-coated catheters). As exposure to chlorhexidine is highly likely in any surgical setting, several centres routinely test all patients referred with perioperative anaphylaxis for chlorhexidine allergy. In countries adopting this practice chlorhexidine allergy is frequently identified (Krishna 2014, Opstrup 2014).

Chlorhexidine is a highly effective antiseptic with a broad antimicrobial activity, and it has potential benefits over povidone-iodine. It is therefore widely used in healthcare settings and in the community. Sensitisation to chlorhexidine can occur in either setting as chlorhexidine-containing products are found in both environments. (Garvey 2007, Nakonechna 2014). The true prevalence of chlorhexidine allergy remains unknown, but is likely to be increasing. During a ten-year period up to 2004 only 50 cases of IgE-mediated reactions were reported in the medical literature. More recently, 104 cases were reported in four UK specialist centres during the four-year period from 2009 to 2013 (Egner 2017).

Main exposure routes and possible alternatives

Many lubricating gels containing both chlorhexidine and local anaesthetic are used routinely for urological and gynaecological procedures including urethral catheterisation. Lubricating gels without local anaesthetic or chlorhexidine, or containing local anaesthetics without chlorhexidine are available. These may be acceptable in many settings, and it is logical to choose a chlorhexidine-free product where this is acceptable. In cases of suspected or confirmed chlorhexidine allergy, chlorhexidine-containing gels must be avoided.

Central venous catheters may be chlorhexidine-coated and the operator may not be aware of this. This is particularly important, as chlorhexidine-coated central lines may lead to rapid and severe reactions which will progress if the catheter is not removed. It is of even greater concern that a central line may be placed during the management of perioperative anaphylaxis, bringing the possibility of perpetuating or worsening the reaction. For short-term use in low-risk patients, chlorhexidine-free central venous catheters should be considered; there are alternative antimicrobial coatings available for high-risk cases. It should be noted that a recent Cochrane review questioned the efficacy of chlorhexidine-coated venous catheters in preventing clinically important morbidity (Chong 2017).

In dentistry, chlorhexidine-containing products are widely used because of its wide antimicrobial spectrum and efficacy. Chlorhexidine-containing mouthwashes are regarded as the 'gold standard' against which other antiseptic mouthwashes are usually evaluated. Preparations include mouthwash or spray solutions, gel, and impregnated chips for use in periodontal pockets (Pemberton 2012). Hexetidine mouthwash (chlorhexidine-free) is an alternative, but the evidence base supporting it is much weaker and up to now it has been rarely used. In the situation of suspected or confirmed chlorhexidine allergy, hexetidine should be considered. In a systematic review into the use of hexetidine as a preventer of plaque and gingival inflammation, it was found to 'provide better effects regarding plaque reduction than placebo mouthwashes' but to be 'a poor alternative to chlorhexidine' (Afennich 2011). In known or suspected cases of chlorhexidine allergy, alternatives include:

- As a general antimicrobial mouthwash and for oral hygiene: hexetidine mouthwash
- For endodontic irrigation during root canal therapy: sodium hypochlorite solution
- For periodontic pocket irrigation and oral surgery irrigation of 'dry sockets': normal saline.

Increasingly chlorhexidine is used for skin preparation, including preparation prior to surgery or venepuncture. For both indications, alternatives are readily available, including povidone-iodine for skin preparation and alcohol-based swabs for venepuncture.

In previous studies, up to 80% of patients diagnosed with chlorhexidine allergy had already reported a possible chlorhexidine allergy that could have been confirmed prior to their adverse reaction (Garvey, 2001, Nakonechna 2014). This presents an opportunity to reduce the number of cases of perioperative chlorhexidine anaphylaxis by taking and acting upon a thorough preoperative allergy history.

The warning features of a pre-existing chlorhexidine allergy include:

- Allergic-type symptoms during previous medical or dental procedures
- Allergic-type symptoms when using hygiene products at home or at work
- Itch following preoperative antiseptic body wash
- Itch or rash following cannulation or venesection.

Investigation for chlorhexidine allergy is not currently standardised, and sensitivity and specificity of the available allergy tests is not consistent in reports. Testing includes the use of skin prick tests, intradermal tests, and blood tests for allergen-specific IgE and basophil activation. Testing should ideally be performed within six months of the reaction, as levels of specific IgE have been shown to fall over time (Garvey 2007). The concentration of chlorhexidine used for skin testing varies, and as chlorhexidine may be irritant at intradermal testing it is important to ensure that a non-irritant concentration is used (Brockow 2013, Garvey 2007). Egner recommended performing at least two tests when testing for chlorhexidine allergy, since sensitivity may be improved by using skin prick and specific IgE as initial tests, with intradermal testing reserved for cases where both initial tests are negative and there remains a high clinical probability of chlorhexidine allergy (Egner 2017).

Positive allergy tests to other potential culprit agents have been reported in chlorhexidine-allergic patients, including tests for neuromuscular blocking agents (NMBAs), latex, opioids and beta-lactam antibiotics (Egner 2017, Garvey 2007, Opstrup 2014). The reason for this is unclear, but it means that allergy clinics should investigate all potential culprits regardless of an initial positive result to chlorhexidine.

The MHRA issued a medical devices alert (MDA/2012/075) in 2012, detailing action to be taken to reduce allergic reactions relating to all medical devices and medicinal products containing chlorhexidine (MHRA 2012). Trusts/Boards in the UK were tasked to ensure that the required actions were taken. The development of trust policies was part of that required action.

Numerical analysis

The NAP6 review panel identified 18 cases of chlorhexidine anaphylaxis, accounting for 9% of culprits, making chlorhexidine the third-commonest trigger for perioperative anaphylaxis after antibiotics and NMBAs.

The Allergen Survey identified 2,298,567 annual exposures to chlorhexidine by at least one route, with 73.5% of all patients being exposed (Chapter 9, Allergen Survey). Based on these data, the incidence of anaphylaxis to chlorhexidine is 0.78 per 100,000 exposures – although this may be an overestimate as the denominator data probably underestimates perioperative chlorhexidine exposure.

Among the 18 cases, nine were Grade 3, eight Grade 4 and one was fatal. Sixteen of eighteen cases occurred in males, which is consistent with published data. Age and ASA grade were similar to the main dataset, though there were no ASA 1 patients. Predominant surgical specialties were: urology (six cases), cardiac and orthopaedics (three cases each).

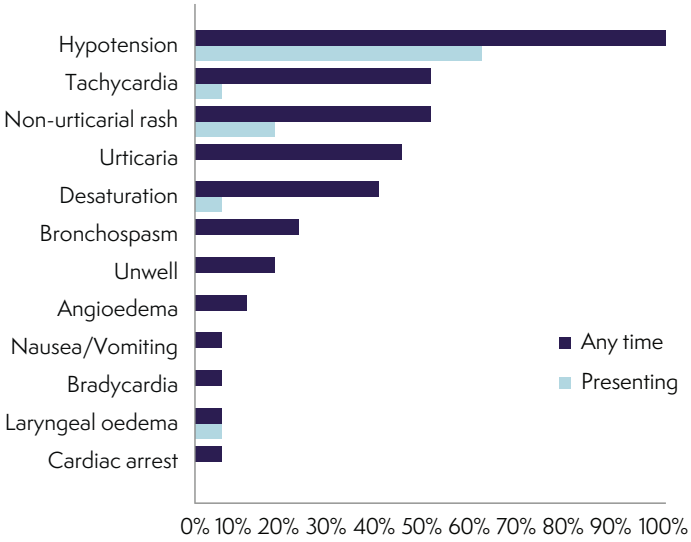
Six cases had only a single reported route of chlorhexidine exposure before the onset of anaphylaxis, while four cases had two and eight had three. Routes of exposure included skin preparation for peripheral cannulation (ten cases), neuraxial block (seven cases) or surgery (four cases), coated central venous catheter (six cases)

and urethral gel (eleven cases). There were no cases where the only recorded chlorhexidine exposure was skin preparation for peripheral venous cannulation.

Time to onset and grade of reaction varied by route of exposure, with quicker onset and higher grade in those with exposure via a coated central venous catheter (mostly onset <5 minutes of exposure and Grade 4) than in those with only topical surgical-site exposure (mostly onset at ≈1 hour and Grade 3).

The presenting clinical features and those occurring at any time during the episode are shown in Figure 1. Approximately two thirds of cases presented with hypotension and none presented with bronchospasm. Bronchospasm was seen in only four (22%) cases compared to 49% of all cases in the main dataset.

Figure 1. Presenting features and those occurring at any time during chlorhexidine-induced anaphylaxis



The anaesthetist considered chlorhexidine to be the cause in only five (28%) of the cases.

One patient was exposed to chlorhexidine and developed anaphylaxis despite reporting chlorhexidine allergy preoperatively. In another case a patient reported a prior reaction during anaesthesia that was not investigated, and reacted to chlorhexidine when exposed. In a third case, after the anaphylactic event reported to NAP6, which was investigated and identified and confirmed to be due to chlorhexidine, the patient had a second procedure during which they were again exposed to chlorhexidine and experienced a further reaction.

In two of six cases of chlorhexidine anaphylaxis due to a chlorhexidine-coated central venous line, the line was not removed during resuscitation.

The testing modalities used by allergy clinics, summarised here, are fully described in Chapter 14, Investigation.

Sixteen patients had serial tryptase samples, and all met the NAP6 criteria for a dynamic tryptase rise. One patient did not have a baseline sample taken, but the acute sample level was above the NAP6 cut off, making it compatible with anaphylaxis (discussed further in Chapter 14, Investigation). One patient had no tryptase samples taken. The mean change from lowest to highest tryptase was relatively modest at 15.8 mcg/L across the 16 cases, and this is discussed further in Chapter 14. The magnitude of the tryptase rise did not relate to the grade of the event.

Seventeen of the cases were investigated in an allergy clinic. Investigation occurred up to 160 days after the event. In the eighteenth case, which was fatal, no blood sample for specific IgE was taken. The investigations carried out are summarised in Table 1.

Table 1. Allergy testing results in cases of chlorhexidine anaphylaxis *there were no equivocal results

Test modalities	Number	Positive*
Skin prick testing only	7	6
Skin prick testing and IgE	3	3 (both tests)
Skin prick testing, intradermal testing and IgE	3	2 (all tests) 1 (IDT & IgE)
IgE only	2	2
Intradermal testing only	1	1
Intradermal testing and IgE	1	1 (both tests)

Only seven (41%) of the cases had more than one test as recommended (Egner 2017). In three (16%) cases, more than one trigger agent was identified.

Discussion

The NAP6 Allergy Survey showed that almost three quarters of patients are exposed to chlorhexidine perioperatively (Chapter 9) – and even this is likely to be an underestimate.

Chlorhexidine is not yet generally considered to be among the 'mainstream' causes of perioperative anaphylaxis, despite evidence to the contrary. This is reflected in failure to investigate appropriately based on perioperative history, in the low suspicion rate we observed when anaphylaxis occurred, in failure to remove chlorhexidine-coated central lines during events, and in patients experiencing second events even after chlorhexidine allergy was identified.

Chlorhexidine anaphylaxis appeared avoidable in three of 18 cases – a considerably higher proportion than in the main dataset. In patients presenting for anaesthesia who had experienced previous perioperative anaphylaxis, chlorhexidine may have been the trigger agent. A thorough preoperative allergy history can reduce the incidence of chlorhexidine anaphylaxis, but only if a positive history is heeded and clinical staff are aware of which medical products and devices contain chlorhexidine.

Any patients with possible warning features should be managed as chlorhexidine allergic and referred to an allergy clinic for further investigation. If the previous reaction occurred during general anaesthesia and it was not investigated, the patient should be referred to an allergy clinic providing perioperative anaphylaxis assessment services. Planned procedures may proceed, but chlorhexidine-free precautions need to be followed. This requires scrupulous attention to the content of all products used on or in the patient.

Despite the 2012 MHRA alert relating to chlorhexidine-containing medical products (MHRA 2012), it appears that many clinical staff are unaware of which products contain this antiseptic, and do not understand the risks of anaphylaxis. Chlorhexidine-coated central venous catheters pose a particular risk, and it is desirable that their chlorhexidine content is clearly and prominently marked.

Products containing chlorhexidine do not currently carry a chlorhexidine allergy warning, and it is very difficult to maintain a complete list of chlorhexidine-containing products. In cases of known or suspected chlorhexidine allergy, any item administered or used for cleaning needs to be scrutinised. An illustrative list from one trust in the UK (Appendix 1) includes many of the pharmaceutical products that contain chlorhexidine. The list of ingredients of all pharmaceutical products and cleaning agents should be checked prior to administration or use on patients with known or suspected chlorhexidine allergy.

It is unsurprising that reactions were more rapid and severe when a central line was the source of the chlorhexidine and the allergen was delivered directly to the circulation. Removing the central line is a key step to treating the reaction under these circumstances, but this requires recognition of the problem and this was not consistently done in NAP6 cases.

National and international guidelines on the investigation of perioperative anaphylaxis do not mandate testing for skin antiseptics but do recommend testing for all relevant exposures. As antiseptics can be 'hidden' on the anaesthetic chart and from the operator, it is pragmatic to include testing for these agents routinely in all cases of perioperative anaphylaxis, as exposure is highly likely (Ewan 2010, Harper 2009, Krøigaard 2007, Mertes 2011). In NAP6, investigation of perioperative anaphylaxis frequently omitted investigation of chlorhexidine (see also Chapter 14, Investigation). When chlorhexidine was tested for, the desirable two tests and testing for other sensitisers was commonly not performed (see also Chapter 14, Investigation).

Although specific IgE testing for chlorhexidine allergy has a sensitivity of around 70% (Egner 2017), this test could help determine the cause of the event in fatal perioperative anaphylaxis. This was not performed in any fatal cases reported to NAP6. A recent preoperative blood sample, for example, one taken for biochemistry, haematology or cross-match purposes, is suitable for use in specific IgE testing.

Recommendations

National

- The MHRA should work with manufacturers of medical devices, eg. central venous (and other intravascular) catheters to ensure that products are labelled clearly and prominently, to identify whether they contain chlorhexidine or not.

Institutional

- Operating theatres should have an accessible list of chlorhexidine-containing items. Appropriate alternatives should be available for patients with suspected or confirmed chlorhexidine allergy
- Investigation of suspected perioperative anaphylaxis should include chlorhexidine
- More than one test for chlorhexidine is necessary to exclude allergy
- When allergy testing for chlorhexidine is positive during investigation of perioperative anaphylaxis, all other potential culprits should still be investigated, as there may be more than one sensitisation.

Individual

- Chlorhexidine allergy should be included in the allergy history taken by anaesthetists, nurses and other healthcare professionals
- Clinical teams should be aware of 'hidden chlorhexidine' such as in urethral gels and coated central venous catheters, and should consider this as a potential culprit if perioperative anaphylaxis occurs
- When anaphylaxis occurs following recent insertion of a chlorhexidine-coated central venous catheter, this should be removed and, if appropriate, replaced with a plain one.

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Appendix 1:

Products containing chlorhexidine: example from one trust performed in 2012/13

Product	Manufacturer	Ingredients	Indication
Acriflex	Thornton & Ross	Chlorhexidine gluconate	Wounds; burns; scalds
Bactigras	Smith & Nephew	Chlorhexidine acetate	Wounds
Cathejell with Lidocaine	Mediplus	Chlorhexidine hydrochloride lidocaine hydrochloride	Urethral catheterisation
Cepton	LPC	Chlorhexidine gluconate	Acne
ChloraPrep	CareFusion	Chlorhexidine gluconate isopropyl alcohol	Skin disinfection
Chlorohex	Colgate-Palmolive	Chlorhexidine gluconate	Mouth infections and hygiene
Clearasil Pore Cleansing Lotion	Crookes Healthcare	Chlorhexidine gluconate alcohol	Acne
Corsodyl	GSK Consumer	Chlorhexidine gluconate	Mouth infections and hygiene
Covonia Throat Spray	Thornton & Ross	Chlorhexidine gluconate lidocaine hydrochloride	Sore throat
Curasept	Curaprox	Chlorhexidine	Oral hygiene
Cyteal	Pierre Fabre	Chlorhexidine gluconate chlorocresol hexamidine isetionate	Disinfection of skin and mucous membranes
CX Powder	Adams	Chlorhexidine acetate	Skin disinfection
Dermol	Dermal Laboratories	Chlorhexidine hydrochloride Benzalkonium chloride liquid paraffin isopropyl myristate	Dry and pruritic skin disorders
Eczmol	Genus	Chlorhexidine gluconate	Soap substitute
Elgydium	Ceuta	Chlorhexidine gluconate	-
Eludril	Pierre Fabre	Chlorhexidine gluconate chlorobutanol Mouthwash	Mouth and throat disorders

Product	Manufacturer	Ingredients	Indication
Eludril	Pierre Fabre	Chlorhexidine gluconate tetracaine hydrochloride (Throat spray)	Mouth and throat disorders
Germolene (06-Dec-2002)	Bayer Consumer	Chlorhexidine gluconate Phenol	Burns; skin irritation; wounds (Cream)
Germolene	Bayer Consumer	Chlorhexidine gluconate Phenol	Burns; wounds; skin irritation
Hibi	Molnlycke	Chlorhexidine gluconate isopropyl alcohol	Hand and skin disinfection (Topical spray)
Hibiscrub	Regent Medical	Chlorhexidine gluconate	Skin disinfection
Hibitane	Centrapharm	Chlorhexidine gluconate	Obstetric disinfection
Hydrex	Adams	Chlorhexidine gluconate	Skin disinfection
Instillagel	CliniMed	Chlorhexidine gluconate lidocaine hydrochloride	Catheterisation; endoscopy
Medi-Swab H	SSL	Chlorhexidine acetate isopropyl alcohol	Pre-injection swab
Medi-Wipe	SSL	Chlorhexidine gluconate alcohol	Hard surface disinfection
Mycil	Crookes Healthcare	Chlorhexidine hydrochloride Tolnaftate	Fungal skin infections (topical powder)
Naseptin	Alliance	Chlorhexidine hydrochloride neomycin sulfate	Nasal carriage of staphylococci
Nystaform-HC	Typharm	Chlorhexidine acetate or hydrochloride Nystatin, hydrocortisone	Infected skin disorders
Nystaform	Typharm	Chlorhexidine hydrochloride Nystatin	Fungal and bacterial skin infections (Cream)
Periogard	Colgate-Palmolive	Chlorhexidine gluconate	Mouth disorders
Quinoderm Antibacterial Face Wash	Ferndale	Chlorhexidine gluconate Cetrimide, detergents	Skin cleanser; soap substitute
Savlon Antiseptic Cream	Novartis Consumer	Chlorhexidine gluconate Cetrimide	Skin disinfection
Savlon Antiseptic Liquid	Novartis Consumer	Chlorhexidine gluconate Cetrimide	Skin disinfection
Savlon Antiseptic Wound Wash	Novartis Consumer	Chlorhexidine gluconate	Skin disinfection
Serotulle	SSL	Chlorhexidine acetate	Wounds
Spotoway	Health & Diet Food Co.	Chlorhexidine	Skin irritation and spots
Sterets H	SSL	Chlorhexidine acetate Isopropyl alcohol	Skin disinfection
Steripod Chlorhexidine Gluconate	SSL	Chlorhexidine gluconate	Skin disinfection
Tisept	Medlock Medical	Chlorhexidine gluconate Cetrimide	Skin disinfection
Torbetol	Torbet Laboratories	Chlorhexidine gluconate Cetrimide	Acne
Unisept	Medlock Medical	Chlorhexidine gluconate	Skin disinfection
Uriflex C	SSL	Chlorhexidine gluconate	Urinary catheter care