

Case Report

Anaphylaxis to the chlorhexidine component of Instillagel®: a case series

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Anaphylaxis to chlorhexidine is rare. We report three cases of anaphylaxis attributed to the chlorhexidine component of Instillagel®, presenting after urological surgery, while the patients were in the recovery room. In these cases, the cause of the collapse was not immediately obvious as the presentation was delayed. Anaesthetists should be aware that urethral lubricants may contain chlorhexidine that can trigger anaphylaxis in susceptible individuals. Anaphylaxis should be considered a possible diagnosis when a patient collapses in the recovery room. Investigation of suspected anaphylactic reactions related to anaesthesia is important to try and identify a likely trigger for a reaction and to help prevent further exposure and potential harm.

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Anaphylaxis can be fatal and is likely to recur on re-exposure; anaesthetists should ensure that all suspected anaphylactic reactions are properly investigated with the objective of preventing further exposure and potential harm. We report three cases of collapse in the recovery room after urological surgery in which Instillagel® (CliniMed Ltd, UK) was used as a urethral lubricant. Anaphylaxis should be considered a possible diagnosis when a patient collapses in the recovery room. Because the delayed onset of symptoms can obscure the diagnosis, investigation should include routine testing for allergy to chlorhexidine. In these three cases, skin prick tests (SPTs) suggested that the chlorhexidine component of the lubricant was the trigger for these three reactions. Subsequent domestic exposure to chlorhexidine can trigger repeat reactions. The patients were referred to the Anaesthetic Reaction Clinic at Manchester Royal Infirmary (Central Manchester and Manchester Children's University Hospitals NHS Trust), where they were investigated jointly by a Consultant Anaesthetist (N.H.) and a Consultant Clinical Immunologist (R.P.).

Case 1

A 33-yr-old male presented for an elective urethrotomy under general anaesthesia. Preoperative assessment revealed no significant medical problems. The patient gave a history

of conjunctivitis on exposure to cats and intermittent acute urticaria which was in a quiescent phase. General anaesthesia was induced with propofol and remifentanyl, a laryngeal mask airway inserted, and maintenance of anaesthesia was with a propofol and a remifentanyl infusion. Tramadol, ketorolac, and gentamicin were given during the procedure. The intraoperative course was entirely unremarkable and at the end of the procedure, a urinary catheter was inserted with Instillagel® per urethram to facilitate the passage of the catheter. Emergence from anaesthesia was uneventful. The patient was transferred to the recovery room where 5 min later, he became unconscious, with an unrecordable arterial pressure and a tachycardia of 119 beats min⁻¹. His oxygen saturation decreased progressively over the next 2 min to 42%. The patient also demonstrated marked cutaneous flushing. The diagnosis of anaphylaxis was suspected and he was promptly resuscitated. Oxygen 100% was administered. Epinephrine to a total of 400 µg and Gelofusine 1000 ml were given i.v. His condition improved rapidly over the next 10 min, and hydrocortisone 100 mg and chlorpheniramine 10 mg were given. He was admitted to the high dependency unit for overnight observation. The patient made a full recovery with no apparent sequelae.

Blood samples for mast cell tryptase (MCT) were obtained at 1, 4, and 16 h after the event, and were markedly

elevated at 1 and 4 h (95.8 and 42.8 $\mu\text{g litre}^{-1}$) indicating mast cell degranulation. At 16 h, the MCT concentration had decreased to within normal limits (9.8 $\mu\text{g litre}^{-1}$).

The patient was referred to the Anaesthetic Reaction Clinic (ARC) for further investigation of this reaction. SPTs for histamine hydrochloride (positive control), chlorhexidine 0.05%, chlorhexidine 0.25%, and cat pelt extract demonstrated a wheal of 2 mm greater than a reaction to normal saline (negative control) and were deemed positive. SPTs for lidocaine 2%, ketorolac, tramadol, and latex were all negative. It seems most likely that the cardiovascular collapse of this patient was caused by the chlorhexidine component of Instillagel[®], used to facilitate the passage of a urinary catheter.

Case 2

A 39-yr-old female presented for cystodistension and optical urethrotomy under general anaesthesia. Preoperative assessment revealed that she had well-controlled asthma and was otherwise fit and well. The patient declared that she was allergic to either cyclizine or Augmentin[®] (GlaxoSmithKline). During spinal anaesthesia for gynaecological surgery 2 yr earlier, she had developed bronchospasm, facial oedema, and generalized erythema, which appeared to coincide with the administration of cyclizine and Augmentin[®] and had been attributed to one of these two drugs.

General anaesthesia was induced with fentanyl and propofol, a laryngeal mask airway inserted, and anaesthesia was maintained with sevoflurane in oxygen and nitrous oxide. Tramadol, ketorolac, and gentamicin were administered. At the end of the procedure, Instillagel[®] was instilled per urethram into the bladder. The intraoperative course and emergence from anaesthesia were unremarkable. The patient was transferred to the recovery room where 20 min into her recovery it was noted that she was flushed with marked urticaria all over her body. She complained of difficulty in breathing, although her oxygen saturation was 99% on supplemental oxygen. An allergic reaction was suspected and chlorphenamine 10 mg and hydrocortisone 100 mg were administered. Fifteen minutes later, the patient became tachycardic (138 beats min^{-1}) and hypotensive (68/38 mm Hg). I.V. epinephrine (100 μg) followed by i.m. epinephrine (500 μg) were given. Ten minutes later, her arterial pressure had returned to preoperative levels (130/79 mm Hg) with a heart rate of 103 beats min^{-1} . Oxygen saturation remained at 99% and her breathing felt easier. The patient was admitted to a ward for close observation and she was discharged home 48 h later. The patient made a full recovery with no apparent sequelae.

Blood samples for MCT were obtained at 1 and 16 h post-event. Both these samples were within normal limits (5.4 and 2.7 $\mu\text{g litre}^{-1}$).

The patient was referred to the ARC for investigation. SPTs for histamine hydrochloride (positive control) and

chlorhexidine 0.05% demonstrated a wheal reaction of 2 mm greater than that to normal saline (negative control) and were deemed positive. SPTs to Instillagel[®], amoxicillin, gentamicin, and latex were negative. A repeat SPT for chlorhexidine was positive. It was concluded that there was a high probability that the collapse was caused by anaphylaxis to the chlorhexidine in Instillagel[®] applied per urethram at the end of the surgical procedure.

Case 3

A 61-yr-old male presented for removal of a ureteric stent under general anaesthesia. Past medical history revealed essential hypertension which was well controlled with ramipril. He had undergone uneventful insertion of a ureteric stent 2 months previously. There was no past history suggestive of allergy. General anaesthesia was induced with fentanyl and propofol, a laryngeal mask airway inserted, and maintained with isoflurane in oxygen and nitrous oxide. Ondansetron and dexamethasone were given as anti-emetics. Cefuroxime and gentamicin were also administered. At the end of the surgical procedure, Instillagel[®] was used per urethram to facilitate passage of a urinary catheter. The intraoperative course and emergence from anaesthesia were entirely unremarkable. The patient was transferred to the recovery room. Ten minutes later he became hypotensive (83/40 mm Hg) and had developed widespread erythema and urticaria. Chlorphenamine 10 mg was administered with Gelofusine 500 ml. The arterial pressure returned to normal values over the next 10 min and the rash and urticaria began to settle. There was no respiratory compromise during this reaction. No blood samples were obtained for MCT after these events. The patient was discharged from hospital with no apparent sequelae.

The patient was referred to the ARC for investigation. SPTs were performed for fentanyl, ondansetron, propofol, cefuroxime, gentamicin, Gelofusine, and chlorhexidine. The SPT for chlorhexidine was positive. All the other SPTs were negative. Intradermal testing for Gelofusine was negative. It was possible to conclude with a high degree of probability that the patient had suffered an anaphylactic reaction to the chlorhexidine component of Instillagel[®] (Table 1).

Discussion

Chlorhexidine is a synthetic cationic bis-biguanide, introduced in 1954, and is in widespread use as a disinfectant and antiseptic in medical and non-medical environments. In the community, chlorhexidine is found in many commercially available products, such as mouthwashes, antiseptic creams, and disinfectant solutions. Clinically, chlorhexidine is used in alcoholic or aqueous solutions of 0.05–4%, for preparation of skin before invasive procedures, and as a disinfectant hand wash. Chlorhexidine is also present in potentially hidden forms, such as a bactericidal coating for central venous catheters or as a component of urethral

Table 1 Summary of the reactions

Patient	Surgery	Presentation	Clinical features of reaction	Severity of reaction	Previous relevant history	Investigation	Causative agent
Case 1: 33-yr-old male	Elective urethrotomy	Collapse in recovery room after procedure	5 min into recovery—unrecordable arterial pressure, hypoxia, unconscious, marked flushing	Grade IV	Intermittent acute urticaria	Positive SPT to chlorhexidine. Plasma tryptase levels raised	Instillagel®
Case 2: 39-yr-old female	Bladder stretch and optical urethrotomy	Collapse in recovery room after procedure	20 min into recovery—hypotension, tachycardia, bronchospasm, flushing, urticaria	Grade III	Bronchospasm, urticaria, and facial oedema during gynaecological surgery 2 yr previously	Positive SPT to chlorhexidine. Plasma tryptase within normal limits	Instillagel®
Case 3: 61-yr-old male	Removal of ureteric stent	Collapse in recovery room after procedure	10 min into recovery—hypotension, flushing, urticaria	Grade III	None	Positive SPT to chlorhexidine. Plasma tryptase levels not measured	Instillagel®

lubricants. Instillagel® contains chlorhexidine 0.25%, lidocaine 2%, methyl hydroxybenzoate 0.06%, and propyl hydroxybenzoate 0.025% formulated as a gel; it is a commonly used antiseptic and anaesthetic lubricant. The Summary of Product Characteristics relating to Instillagel® advises against its use in individuals with known hypersensitivity to chlorhexidine, but only the lidocaine component is described as causing undesirable effects.¹

Chlorhexidine use appears to be increasing. There is good evidence to show that chlorhexidine is more effective in preventing infection as compared with more traditional povidone-iodine solutions.² Recent national UK guidelines commissioned by the Department of Health advocate the use of chlorhexidine 2% in isopropyl alcohol 70% as the skin disinfectant of choice for central venous catheter insertion and for urethral catheterization. The use of a urethral lubricant for catheterization is also suggested.³ Many locally agreed guidelines and protocols recommend the use of chlorhexidine containing products.

Chlorhexidine is a potentially immunogenic substance and can cause hypersensitivity reactions; typically contact dermatitis, contact urticaria, or photosensitivity. Rarely, chlorhexidine may trigger allergic anaphylaxis. The first case was described in 1985.⁴ Anaphylaxis to a chlorhexidine-containing gel was first reported in 1992.⁵ Since then, several cases have been described predominately in the urological literature.^{6–10} All the previous reported cases of anaphylaxis to the chlorhexidine component of a lubricant were reported in male patients. Many of the reports of chlorhexidine anaphylaxis describe milder non-specific reactions with previous exposure to chlorhexidine.¹¹ None of the cases in the current series demonstrated this pattern, even on close direct questioning.

These cases highlight several important points. The ubiquitous and increasing use of chlorhexidine containing products may result in sensitization to chlorhexidine. Consequently, life-threatening allergic reactions to chlorhexidine may become more common. Studies, however, have shown considerable geographical variation in sensitization to chlorhexidine. A Swiss study showed that up to 2% of their population are sensitized to chlorhexidine.¹² A Japanese study of health-care workers found over 7% describing contact dermatitis with chlorhexidine.¹³ In contrast, a Danish study failed to demonstrate any evidence of type I or type IV allergy to chlorhexidine in a group of health-care workers.¹⁴ This is a surprising result as chlorhexidine is reported as the most common cause of anaphylaxis related to anaesthesia in Denmark; responsible for more than 13% of reported reactions.¹⁵ The sample sizes for both studies were, however, small. Other published series of anaphylaxis related to anaesthesia have not identified chlorhexidine as a cause of reactions.^{16 17}

Several factors conspire to confound the clinical diagnosis of anaphylaxis to chlorhexidine: delayed presentation, the fact that chlorhexidine is not a drug administered by an anaesthetist and that it may be present in a covert form,

all make it easy to overlook anaphylaxis to chlorhexidine as a cause of cardiovascular collapse. These cases are a reminder that life-threatening reactions can occur in the postoperative period after completely uneventful anaesthesia and anaphylaxis must be considered in any case of unexplained cardiovascular collapse in the recovery room. Other authors have described a typically delayed presentation involving allergic reactions to chlorhexidine.^{9–11} This is an unusual feature compared with other anaphylactic reactions related to anaesthesia which typically present within minutes of the administration of a drug. This delay in presentation of chlorhexidine allergy means that even with repeated reactions at home the cause may not be recognized: thus, it is possible that the previous intermittent acute urticaria of the first case may have been caused by domestic exposure to chlorhexidine in cosmetics or household agents.

Our second case further highlights the importance of the thorough investigation of unexplained reactions related to anaesthesia by a specialized team. In the presence of plasma MCT levels within normal limits, it is tempting to exclude allergic anaphylaxis as a cause for this reaction. However, it is well documented that a severe anaphylactic reaction can occur without a detectable increase in plasma MCT levels. It is thought that in these cases a mechanism of basophil degranulation rather than the more typical mast cell activation is responsible.¹⁸ Basophils contain up to 700-fold less tryptase than mast cells which may explain why there is no significant increase in MCT detected in plasma. The majority of reactions do see an increase in plasma MCT and collecting appropriately timed samples for plasma MCT remains an essential part of the investigation of a suspected anaphylactic reaction.

Another potentially misleading result from the investigation of the second case was the negative SPT to Instillagel[®]. This can be attributed to the presence of lidocaine within the gel which will ablate the neurogenic wheal response required for a positive SPT. Subsequent testing with chlorhexidine in isolation did yield a characteristic positive result. Although the timing of the original reaction appeared to coincide with the administration of either Augmentin[®] or cyclizine, and despite the normal plasma MCT levels and negative SPT to Instillagel[®], it seems probable that this initial reaction was due to the chlorhexidine component of Instillagel[®]. Investigation of the original reaction at the time may well have identified chlorhexidine as the cause and this knowledge may well have prevented further exposure and her subsequent life-threatening reaction. A recent case in law found against an anaesthetist in a similar case involving neuromuscular blocking agents. The judge found that an anaesthetist has an obligation to investigate suspected adverse drug reactions. This judgement was upheld at appeal.¹⁹ The correct identification of the cause of an allergic reaction related to anaesthesia is difficult even in a specialized Anaesthetic Reaction Clinic. Patients can be exposed to many potential allergens throughout the course of a procedure and symptoms related to chlorhexidine

allergy may present up to 40 min after exposure. The assumption that a drug given immediately before a reaction is the actual culprit drug is unwise. We support the contention that investigation of any suspected anaphylactic reaction in the intraoperative or postoperative period should include testing for chlorhexidine allergy.¹¹

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