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ORIGINAL ARTICLE

Immediate hypersensitivity to chlorhexidine is increasingly recognised in the United Kingdom

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Abstract
Background: Chlorhexidine is widely used as an antiseptic agent. It is a potentially allergenic substance that can cause severe hypersensitivity reactions.
Objective: We describe six patients who had anaphylactic reactions attributed to chlorhexidine during surgery. These patients were exposed to chlorhexidine in gels, swabs and catheters.
Materials and methods: Six patients from three UK centres with clinical history suggestive of anaphylaxis during surgery are reported. Detailed history, review of case notes, determination of chlorhexidine specific IgE, mast cell tryptase and skin tests were performed.
Results: On detailed assessment five of six patients demonstrated a previous history of reactions on re-exposure to chlorhexidine. All six patients had elevated specific IgE to chlorhexidine. Skin prick test with chlorhexidine was performed in four of the six patients and was found to be positive.
Conclusion: Immediate hypersensitivity to chlorhexidine appears to be common but underreported in the UK. We recommend that centres investigating patients with reactions during anaesthesia and surgery should routinely include testing for chlorhexidine allergy.

Introduction

Chlorhexidine is widely used in many different preparations because of its antimicrobial properties. However, it is a potentially allergenic substance, adverse reactions to which have been described in the literature for the past 30 years. Most of these reactions have been limited to the skin and were mild in severity.[1–4] Type I hypersensitivity reactions, including anaphylaxis, have been reported since 1984,[5] but are considered to be rare. Indeed during a ten-year period only 50 case reports of chlorhexidine-related anaphylaxis have been published.[6] However, a high rate of reactions to chlorhexidine was reported in Japan and as

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a result specific recommendations regarding the maximum chlorhexidine concentration to be used were issued.[7]

There are a number of case reports describing IgE-mediated anaphylactic reactions to chlorhexidine, mostly related to anaesthesia and surgery.[8–11] However the true incidence of anaphylaxis to chlorhexidine is not known and it is likely to be underestimated. In this manuscript, we describe six patients from three UK centres who have had anaphylactic reactions when exposed to chlorhexidine during surgery.

Materials and methods

Six patients from three UK centres with clinical history suggestive of anaphylaxis during surgery were investigated 6 weeks after the reaction. Informed consents were obtained from all patients. The assessment of these patients was perrofmed according to a standardised protocol in each centre and included detailed history, review of case notes, determination of total and specific IgE to chlorhexidine and other drugs used during anaesthesia, and mast cell tryptase. In addition, skin tests with chlorhexidine, latex and drugs listed in the anaesthetic record (in some case an alternative agent from the same group was used e.g. NMBA); with the exception of inhalational agents were also carried out.

The investigations were conducted in accordance with the principles of the Declaration of Helsinki and the Good Clinical Practice Guidelines as issued by the International Conference on Harmonisation (ICH E6, 1996).

Case 1

A 50-year-old man with a history of ischaemic heart disease presented for coronary artery bypass graft surgery under general anaesthesia. There was no other significant past medical or surgical history. He had no history of atopy. General anaesthesia was induced with fentanyl, etomidate, pancuronium and maintained with an air/oxygen/isoflurane mixture. Cefuroxime was given at the beginning of the procedure and the airway was secured with a Portex endotracheal tube. A central venous catheter was inserted and an infusion with saline and then Volprex was commenced. Ten minutes after insertion of the central line the patient developed flushing, an urticarial rash on his legs, facial swelling and had hypotension (70/40 mm Hg) and tachycardia (146 beats/min). His oxygen saturation was 90% while on 100% oxygen ventilation. A diagnosis of anaphylaxis was suspected and he was promptly resuscitated. Volprex was thought to be the culprit and was discontinued. He did not respond to i.v. metaraminol or phenylephrine and was treated with bolus dose and then infusion of noradrenalin (NA). After 10 min his blood pressure and pulse returned to normal and the operation continued.

He had a further reaction in the recovery room with hypotension, tachycardia and generalised urticaria. Central line catheter was withdrawn at this stage. He was treated with i.v. chlophenamine (10 mg) and hydrocortisone (100 mg) and maintained on small dose of i.v. NA for 12 h and he subsequently made a good recovery. Blood samples taken for mast cell tryptase at 1, 2, and 12 h after the event showed raised levels at 1 and 2 h (17.3 and 20.2 respectively; normal range 0–14 mcg/L). At 12 h the MCT level returned to normal (7.1 mcg/L).

The patient was referred to the allergy clinic where he underwent detailed assessment. Specific IgE for chlorhexidine was markedly raised at 30 kUA/L (normal <0.35). Specific IgE for latex, suxamethonium, and quaternary ammonium compound were negative. Skin prick and intradermal tests with cefuroxime and suxamethonium were negative.

It is most likely that the anaphylactic reaction experienced by this patient was caused by chlorhexidine in the impregnated central line catheter.

Case 2

A 78-year-old man with a history of ischaemic heart disease presented for an angiogram with contrast. Anaesthesia was induced with midazolam, fentanyl, and propofol and maintained with an air/oxygen/isoflurane mixture. Ten minutes into the procedure he developed breathlessness and generalised urticaria. He was treated with i.v. chlophenamine and hydrocortisone and subsequently made a good recovery. He was not referred for further investigations and was labelled as having a ''reaction to the angiogram dye''. No investigations were performed during the reaction.

Few months later, he underwent an angioplasty and because of his previous reaction he was pre-medicated with prednisolone. The anaesthesia was induced with midazolam, fentanyl and propofol and maintained with an air/oxygen/isoflurane mixture. However, 10 min later he developed generalised urticaria and breathlessness that responded well to i.v. chlorphenamine and hydrocortisone and the procedure was abandoned. Blood samples taken 1 h after the event showed normal level of mast cell tryptase (4.6 mcg/L).

He was referred to the allergy clinic for further assessment. On review it was revealed that he had had generalised urticaria in the past on exposure to Corsodyl mouthwash, which contains chlorhexidine. Specific IgE to chlorhexidine was positive at 2.3 kUA/L while IgE to latex, iodine, pholcodine and skin test to lidocaine were all negative.

It was concluded with a high degree of certainty that the cause of his reaction on both occasions was allergy to chlorhexidine. We recommended chlorhexidine avoidance and the patient subsequently had a successful angioplasty.

Case 3

A 72-year-old male presented for cystoscopy under general anaesthesia. Pre-operative assessment had revealed no significant medical problems and no history suggestive of atopy. General anaesthesia was induced with fentanyl, propofol, ondansetron and the maintained with isoflurane in oxygen and nitrous oxide. Gentamicin was given during the procedure and the intraoperative course was entirely unremarkable. At the end of the procedure, Instillagel® (chlorhexidine gluconate 0.25% and lidocaine 2%) was used to facilitate the passage of a urinary catheter and the patient was transferred to the recovery room. Ten minutes later, he developed hypotension (73/40 mm Hg), tachycardia (102 beats/min) and generalised urticaria. He had no