BMJ Case Reports

Unexpected outcome (positive or negative) including adverse drug reactions

Near fatal intra-operative anaphylaxis to chlorhexidine—is it time to change practice?

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Summary

The authors report a case of a near fatal anaphylactic reaction to chlorhexidine. Increasingly adverse reactions are being reported with the use of chlorhexidine. Serious reactions are related to use on mucous membranes and acceptable alternatives are readily available. Therefore, the fundamental question that must be asked is: is it time to withdraw chlorhexidine preparations used for mucous membranes?

BACKGROUND

Chlorhexidine is used widely in different preparations for its antiseptic properties. The potential for developing sensitivity to chlorhexidine is very high as it is commonly used by the general population in mouthwash, toothpaste and skin disinfections. We report a case of a near fatal anaphylactic reaction to chlorhexidine. Subsequent skin testing suggests sensitivity to chlorhexidine, which had been used in the form of Instillagel (CliniMed, High Wycombe, UK) for urethral lubrication.

CASE PRESENTATION

A 49-year-old man presented for cystolithotripsy. He had a history of rheumatoid arthritis with recurrent renal and bladder stones. He was a chronic smoker and had no known allergies. Previous anaesthetics (general and spinal) were uneventful. Anaesthesia was induced and maintained with propofol and remifentanil. A laryngeal mask airway (LMA) was used to secure the airway. Intraoperatively he received ciprofloxacin, gentamicin, diamorphine, hyoscine butylbromide (buscopan) and ondansetron. Fifty minutes from the start of anaesthesia, the patient developed unexplained tachycardia associated with a drop in saturation (89%) and $ETCO_2$ (2.5 kpa). The LMA was changed to an endotracheal tube. The patient continued to desaturate, which was followed by pulseless electrical activity (PEA). Cardiopulmonary resuscitation was initiated rapidly and the patient received three doses of epinephrine (1 mg each) and one dose of atropine (1 mg). The PEA changed to ventricular fibrillation for which the patient was defibrillated. This was followed by a normal sinus rhythm. An epinephrine infusion was started to maintain the blood pressure. He was ventilated over night. Blood samples were sent for troponin-T and mast cell tryptase assays. He made an uneventful recovery and he was extubated next day. The mast cell tryptase level was elevated to 73 µg/litre (normal <11.4 µg/litre) supporting the diagnosis of anaphylactic reaction. Troponin-T (1.03 ng/ml) was raised, which could have resulted from cardiopulmonary resuscitation. A CT pulmonary angiography showed no evidence of an embolus.

OUTCOME AND FOLLOW-UP

Three months later the patient underwent a skin prick test for propofol, latex, cefuroxime, augmentin, ciprofloxacin, gentamicin and chlorhexidine. Skin prick testing for chlorhexidine was positive. Subsequently, after 20 months, skin prick test for chlorhexidine and latex was equivocal. Blood samples were tested for total IgE and specific IgE for latex. Total IgE was raised 202 ku/litre (normal <100 ku/litre) and specific IgE for latex was 0.06 IU/ml of grade 0 (insignificant). A specific IgE test for chlorhexidine is not available. The basophil activation tests were negative for both chlorhexidine and latex. With these tests it was concluded that the most likely cause of anaphylactic reaction to this patient was chlorhexidine.

On review, it was noted that the urologist had used Instillagel to the urethra to facilitate passage of cystoscope. Instillagel contained lignocaine hydrochloride 2.0% and chlorhexidine digluconate 0.25%. The patient was advised to avoid exposure to chlorhexidine preparations and he should be treated in a latex-free environment in future as in 20% of cases skin prick test to latex is negative.

DISCUSSION

Chlorhexidine is a bisbiguanide and widely used as an antiseptic in medical practice as well as in personal hygiene commodities, such as mouthwash, toothpaste and contact lens solutions. Therefore, the potential for sensitisation in the general population and in healthcare workers is as high as 2%.[1] Contact dermatitis is the common adverse effect with chlorhexidine. It can also cause photosensitivity, occupational asthma, gingivitis, discolouration of teeth and distortion of taste. Adverse reactions have been reported with the use of chlorhexidine as a skin disinfectant for surgery, insertion of epidural[2] and central venous catheters[3] and as an antiseptic for mucous membranes.[4] Adverse reactions to chlorhexidine can be

either anaphylactic or anaphylactoid in nature, which are indistinguishable clinically.

Acute anaphylactic reactions to chlorhexidine are very rare and the exact prevalence is unknown. In the UK, the Medicines and Healthcare products Regulatory Agency received 301 reports of reaction to chlorhexidine from 1963 to 2006, of which 5 were fatal. In Japan, there have been 15 reported cases of anaphylactic shock related to the use of chlorhexidine.[5] In 1984, the Japanese ministry of welfare recommended that the use of Chlorhexidine on mucous membranes be prohibited.[5] In 1985, the Japanese manufacturer advised against the use of chlorhexidine on mucous membranes and recommended that chlorhexidine be used on wound surfaces at the lowest bactericidal concentration of 0.05%.[5] The occurrence of adverse reaction to chlorhexidine has raised questions about the risk of sensitisation among healthcare workers. Evidence for use of local anaesthetic lubricant before various forms of transurethral instrumentation is lacking.[6] Acceptable alternative intraurethral gels[6] are lubricant with anaesthetic (eg, Xylocaine; AstraZeneca LP, Wilmington, Delaware, USA) and plain lubricant (eg, K-Y Jelly; Johnson & Johnson Medical, Arlington, Virginia, USA).

Anaphylactic reaction to chlorhexidine in our patient is supported by the clinical features of cardiovascular collapse, marked increase in mast cell tryptase concentration and positive skin prick test. Total IgE was raised but specific IgE for latex is of grade 0. The basophil activation test for latex and chlorhexidine were negative. However, Garvey *et al*[7] described false-positive reaction to chlorhexidine in aqueous solution greater than 0.0002%. Therefore, the validity of positive skin prick test in our patient is debatable. To substantiate our clinical impression we need to measure specific IgE for chlorhexidine, which is currently not available.

Interestingly, the anaphylactic reaction occurred 50 min after the exposure to chlorhexidine and this corresponds to the time reported by Garvey *et al*.[2] Unusually there were no skin manifestations or bronchospasm. A review of clinical features and markers of anaphylactic and anaphylactoid reactions reported that bronchospasm was feature in 43% with proven anaphylactic and 28% in hypersensitivity reactions.[8] The positive skin prick test suggests that systemic absorption occurred when Instillagel was applied for urethral lubrication resulting in acute anaphylactic reaction. An intact epidermis is a barrier to systemic absorption.

Increasingly, adverse reactions are being reported with the use of chlorhexidine. Serious reactions are related to use on mucous membranes. Acceptable alternatives are readily available. Therefore, the fundamental question that must be asked is: is it time to withdraw chlorhexidine preparations used for mucous membranes?

Learning points

- Potential for sensitisation to chlorhexidine is high.
- Severe anaphylactic reactions to chlorhexidine are rare.
- Severe anaphylactic reactions are related to use on mucous membranes.
- Early recognition of the reaction is the key to successful outcome.

Competing interests None.

Patient consent Obtained.

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