Anaphylactic Reaction of Uncertain Cause

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Abstract

Anaphylactic reactions associated with general anaesthesia though rare can be life threatening and caused by administered agents not directly connected to the anaesthetic.

In this case a reaction, which was not immediately recognised as such, was considered most likely due to chlorhexidine but this was not confirmed at further investigation. The management of the case is described and chlorhexidine anaphylaxis reviewed together with a consideration of uncertainty of diagnosis for both patient and anaesthetist.

Clinicians need to be periodically reminded of this important though often hidden risk which can present at a variable time from the stimulus and be of slow onset.

INTRODUCTION

Chlorhexidine has been widely used since 1954 as an antiseptic with a broad spectrum of activity for topical application. A number of anaphylactic reactions have been reported since then, with first symptoms observed from 15 though more usually towards 45 minutes into the operation, produced by the topical application to mucous membranes and skin of a component of what might be considered an ‘innocent' product such as urethral lubricant but still causing a life-threatening event [1,2,3,4].

Widely used in medicine and surgery but practitioners are often not overtly aware of this or its presence in a range of non-medicinal products including lozenges, gargles and toothpaste. Previous exposure and opportunities for sensitisation are, therefore, significant and often multiple episodes occur before chlorhexidine is identified as the culprit [5].

The importance of considering non-anaesthetic causes for anaphylactoid reactions during surgery and maintaining a high degree of suspicion is highlighted.

CASE REPORT

A male patient, aged 61 years, having experienced recurrent urinary tract infections with epididymoorchitis associated with haematuria was submitted to flexible cystoscopy using Instillagel ® (Clinimed, High Wycombe, UK), a mixture of lidocaine hydrochloride 2%, chlorhexidine 0.25%, methylhydroxybenzoate 0.06%, propylhydroxybenzoate 0.025% in propylene glycol, for lubrication which revealed a red area of bladder mucosa. Admitted the night before surgery 2 weeks later for a formal cystoscopic examination, he had no co-morbidities apart from a 45 year smoking history, took no regular medication, was a social drinker and had not previously undergone general anaesthesia. No allergies or relevant family history were reported. Preoperative investigations included serum sodium 139 mmol/l, potassium 4.8 mmol/l, urea 4.9 mmol/l, creatinine 81 micromol/l, haemoglobin 16.4 g/dl, white blood cell count 9.9 x 109/l and platelets 189 x 109/l. Body Mass Index was 25, ECG within normal limits, temp 36.4oC, heart rate 73 beats per minute and blood pressure 132/80.

Last fluids were consumed 10 hours before.anaesthesia was uneventfully induced with propofol 160 mg. preceded by midazolam 2.5 mg. and alfentanil 500 mcg. A size 5 classic laryngeal mask airway (LMA) was inserted and the patient breathed spontaneously a mixture of nitrous oxide, oxygen and enflurane through a Humphrey ADE circuit. Intraoperative monitoring included vapour concentration and the derived MAC value. Analgesia was provided by diclofenac 75 mg. given intravenously as usual practice.

Approximately 30 minutes following induction and temporally associated with unexpectedly increased surgical stimulation, the patient coughed and the subsequent airway disturbance led to a significant fall in SpO_2. The LMA was removed and the cystoscopy was concluded with catheter insertion.

Following this episode SpO_2 remained low associated with significant hypotension of then uncertain cause treated by the infusion of 2L compound sodium lactate solution and titrated intravenous aliquots of metaraminol to 5mg.

On admission to the theatre recovery area now awake, blood pressure had returned to normal (160/70) but with a tachycardia (140 beats per minute[bpm]) and peripheral SpO_2 undetectable. Over the ensuing 15-20 minutes the blood pressure fall back to 65/50 with a heart rate of 115 bpm and SpO_2, which had recovered to 94%, fell to 80%. Advice was sought from a colleague who, as by this time patient had become very erythematous, diagnosed a latex reaction as he had had a similar case himself in the past. Continuing treatment therefore included adrenaline (17ml of 1:10000 in total), hydrocortisone (600 mg in total), chlorpheniramine 10mg and succinylated gelatin (gelofusine® B Braun AG, Melsungen, Germany) 1500ml together with nebulised salbutamol 2.5mg for a wheeze which later developed.

Forty five minutes after admission to the recovery area the patient's haemodynamic parameters had significantly improved and he remained there for 4 hours in total before being transferred back to the urology ward after a review by the consultant anaesthetist on emergency duty, in a good condition with temperature 36.4oC, blood pressure 110/70, heart rate 90 bpm, SpO_2 95% on room air and passing urine normally. Post-operative routine blood tests were all within normal limits.

Blood taken for mast cell tryptase 1½ hours after the start of the reaction showed a level of 219 ng/ml (normal <13), a normal total IgE at 36.8 kU/l with latex specific IgE <0.35 kUA/l (grade 0 - negative). At 24 hours mast cell tryptase had fallen to 19.1 ng/ml.

The patient was referred for further study after latex allergy had been excluded in our local laboratory.

In the regional clinic the consultant allergist performed skin tests for tropical fruit which were negative and latex negativity was confirmed. In addition skin tests for all the drugs as used, propofol, midazolam, alfentanil, diclofenac, ceftriaxone together with chlorhexidine were also negative. The opinion given was that diclofenac (to which the patient had not previously been exposed) might be the culprit whilst a reaction to chlorhexidine remained a possibility.

DISCUSSION

Chlorhexidine is a synthetic cationic linear bis-biguanide (two chlorguanide moieties together) widely used since 1954, usually the gluconate salt, as an antiseptic for topical application with a broad spectrum of activity including mycobacteria, some fungi and some viruses. A number of reactions have been reported since then including 4 out of 68 patients referred the Danish Anaesthesia Allergy Centre over a 3 year period [6]. First symptoms were observed 15-45 minutes into the operation minutes into the operation in these 4 patients in none of whom was chlorhexidine intitially suspected [7].

Immediate and delayed-type reactions can occur but, unusually, it is the whole chlorhexidine molecule that is complementary to the IgE antibody combining sites on the sensitised basophils [8].

Chlorhexidine is typically not considered until a second or later exposure; anaesthetic agents and antibiotics were eliminated as the cause following the first and latex the second with reactions at 35 and 40 minutes in one reported case [9]. In another, after two episodes following urethral procedures for which lignocaine was blamed, a general anaesthetic for Trans-Urethral Resection of the Prostate was embarked upon which after 80 minutes lead to an anaphylactic reaction; chlorhexidine, used as Instillagel® was eventually implicated and confirmed [10]. Chlorhexidine-coated central venous catheters have been implicated and one reported reaction which was thought initially to be due to chlorhexidine in a skin preparation proved to be that in Instillagel® [11,12,13,14].

Topical applications to mucous membranes and skin have lead to reactions, a component of what might be considered an ‘innocent' product or ‘hidden allergen' still able to cause a life-threatening event [1,2,3,5,15]. Anaphylactoid(ic) reactions in anaesthesia are rare, typically starting 30-60 minutes into the anaesthetic. With an incidence of 1:10-20000, 70% are due to neuromuscular blocking drugs with just 2.5% ‘other' including NSAID and chlorhexidine. Skin testing has only been validated for some allergens; in respect of NSAID, they are not useful, and, for chlorhexidine, should be interpreted with caution. Recent reviews also highlight the need for proper investigation and follow up including appropriate advice to patient [16,17]. We know, however, that the many patient reported ‘allergies' are neither anaphylactic nor anaphylactoid reactions [18]. An audit undertaken in our own hospital last year confirmed this: 10% of patients had a

reported and/or documented allergy which was ‘real' in only 5.8% (including anaphylactic reactions 0.6%) but due to recognised side-effects in 4.2%. To this add the uncertainty of often inappropriate advice particularly when not provided by an anaesthetist.

In respect of chlorhexidine, clinicians need to be reminded of this important risk which can present at a variable time from the stimulus and be of slow onset. Exposure to other than the usually suspect anaesthetic agents should be considered particularly when up to an hour has passed [3].

It is not surprising that multiple episodes can occur before the causative agent is identified as anaesthetists often note mild ‘reactions' in the form of flushing or urticaria, ‘histamine release' and rashes or pruritus in the postoperative period to which little importance is attached [5,7].

Though widely used in medicine and surgery, clinicians are often not aware that chlorhexidine is present in a range of non-medicinal products, lozenges, gargles, toothpaste allowing for previous exposure and significant opportunities for sensitisation [5]. The importance of considering non-anaesthetic causes for anaphylactoid reactions during surgery must be highlighted and maintaining a high degree of suspicion emphasised. Clinicians should be reminded that this is an important risk factor attached to many patients (increasing with those of increasing age) who will undergo flexible prior to rigid cystoscopy under general anaesthesia which is often subsequently repeated.

The patient in this report was advised by the allergist to avoid diclofenac completely as this was considered to be suspect and exercise caution with other NSAID but is this appropriate and evidence-based?

The Association of Anaesthetists of Great Britain & Ireland guidance [19] states: ‘It is important to use an allergist with considerable experience of this problem and investigation should preferably be in a defined Regional Allergy Centre' (which recommendation was followed in this case) and, of course: ‘The anaesthetist is responsible for the advice given to patients about future anaesthesia'. The creation of an integrated network to promote a common approach and investigation and avoid the giving of mixed messages to patients must be supported whilst recognising that it's almost worse when you don't have the answer.

Vigilance at all times and wary of the wolf waiting to pounce. Perhaps another application of the acronym MAC standing for Maximum Anesthesia Caution [20].

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