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Platinum Opinion

Chlorhexidine: A New Latex?

Krzysztof Rutkowski*, Annette Wagner

Department of Allergy, Cambridge University Hospitals NHS Foundation Trust, UK

1. Case study

A 73-yr-old man underwent transurethral resection of the prostate under spinal anaesthesia. He had 3 ml of 0.5% bupivacaine (Marcaine Heavy; AstraZeneca, London, UK) administered intrathecally. Block was achieved at T10, and he was transferred to theatre. Systolic blood pressure was 120–130 mm Hg with a heart rate (HR) of 70 beats per minute (bpm). He was given a bolus of 160 mg gentamicin intravenously. Instillagel (lidocaine hydrochloride 2 g/100 g and chlorhexidine gluconate 0.25 g/100 mg; Farco-Pharma GmbH, Cologne, Germany) was used intraurethrally. He received no sedation.

Surgery commenced, and within 5 min, he reported that “things were getting to his head” and requested sedation. Block height was checked, and power in his arms and hands was normal. He received 3 mg midazolam intravenously and was noted to be sweating profusely. He became bradycardic (HR 30 bpm). Surgery was abandoned, and 600 µg atropine was administered intravenously with oxygen via a face mask. Blood pressure was unrecordable, but there was no bronchospasm. Electrocardiogram (ECG) electrodes had detached due to profuse sweating, and there was no femoral pulse. The patient was given 1 mg adrenaline intravenously. Cardiopulmonary resuscitation was commenced. He was intubated. After electrodes had been reattached, ECG showed an HR of 30 bpm. After a further bolus of 1 mg atropine intravenously, circulation returned and HR started to recover. Intravenous fluids (1000 ml 0.9% sodium chloride) and continuous intravenous adrenaline (4 mg in 50 ml over 8 h) were needed to support blood pressure. On-table echocardiography revealed good cardiac function with no regional wall abnormalities. Because a widespread urticarial rash was

noticed, 10 mg chlorphenamine and 200 mg hydrocortisone were administered intravenously.

The patient started to recover, adrenaline was weaned off, and he was extubated and made a full recovery over the next 2 h.

Serum tryptase levels (2–14 µg/ml is normal) after start of reaction were as follows: 62.3 at 50 min, 67.8 at 3 h 5 min, 46.8 at 4 h 21 min, 34.3 at 6 h 55 min, and 8.3 at 24 h 11 min.

An allergic reaction was confirmed, and the patient was referred to the allergy clinic for further evaluation. In the referral letter, only gentamicin and lignocaine were mentioned as possible triggers. Moreover, it was mentioned that he had experienced a *previous, albeit less severe, episode after a flexible cystoscopy* several years previously. No records were available for this event. At the time, a heart attack was suspected but not confirmed, and subsequent cardiac investigations were normal.

Investigations in our drug allergy clinic revealed negative skin prick and intradermal tests to bupivacaine and gentamicin. Skin prick test to chlorhexidine (CHX) was strongly positive at 7 mm, with a positive CHX specific immunoglobulin E (sIgE) of 13.1 kU/l.

A final diagnosis of severe CHX allergy was made. The patient was advised to wear a medic alert bracelet and was given a letter stating his allergy. Moreover, he was informed of CHX as a common component of everyday products and the need to avoid those.

2. Discussion

Antisepsis changed the face of modern medicine, but universal precautions were introduced only in 1985 with the advent of the AIDS epidemic. Latex gloves and topical disinfectants were an essential part of those measures [1].

* Corresponding author. Department of Allergy, Cambridge University Hospitals NHS Foundation Trust, Box 40, Hills Road, Cambridge, CB2 0QQ, UK. Tel. +44 1223 217777; Fax: +44 1223 216953. E-mail address: Rutkowski@doctors.org.uk (K. Rutkowski).

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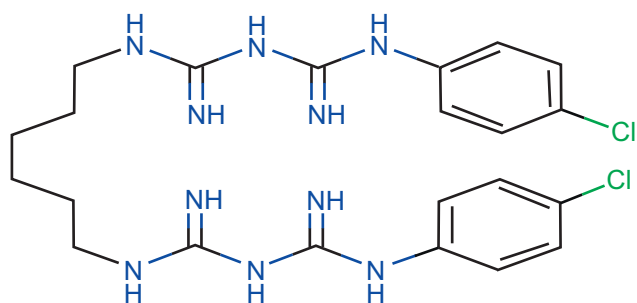


Fig. 1 – Chlorhexidine [2].

Accidental discovery of CHX [2] (Fig. 1) during a quest for a new antimalarial was the beginning of a true success story. This broad-spectrum biocide with a kill rate faster than other antiseptics became available in the United Kingdom as early as 1954. In 1981, the first urologic lubricant with CHX was approved by the US Food and Drug Administration (FDA). Subsequently, CHX became omnipresent in surgery, dentistry, and medicine in mouthwashes, skin preparation, impregnated peripheral and central lines (CHX/silver sulfadiazine) and dressings. It was added to the ventilator care bundle in 2001 [3]. CHX use is now enshrined in the national infection control guidelines [4]. It is also increasingly used in everyday products (Table 1).

There are striking similarities in the timeline of CHX and latex allergy (LA). Nine years after discovery, CHX was recognised as an allergen causing allergic contact dermatitis (delayed, type IV hypersensitivity). Since then, urticaria, photodermatitis, fixed drug eruptions, and occupational asthma have been reported [3–5]. Anaphylaxis (type I, IgE-mediated reaction) was first reported in Japan in the 1980s, but the first case of anaphylaxis after intraurethral exposure was published in 1992 [4,6]. Hypersensitivity reactions to CHX can be very severe, with protracted hypotension or collapse and require aggressive treatment with adrenaline/inotropes [4,7]. UK Medicines and Healthcare Products Regulatory Agency review (1963–2006) identified 301 reports of reactions, with 5 fatalities [4].

Latex anaphylaxis was reported in 1979, and by the early 1990s, LA became a serious concern. Atopy, multiple occupational exposures and surgeries, use of powdered gloves, and mucosal exposure to latex (higher risk of severe

reactions) were identified as risk factors. After the first fatal anaphylactic reaction was reported in 1991, the FDA issued an LA alert [1]. Hospitals started using nonpowdered gloves and nonlatex alternatives; special management plans were put in place. Consequently, from the mid-1990s onwards, a steady decline in the incidence of LA was observed.

Many latex allergens have been identified [1]. CHX epitope mapping suggests that the entire molecule is the allergen (molecular weight 505 daltons), although other allergenic determinants are possible [8]. The majority of cases of anaphylaxis occur in the context of a urologic procedure. The higher risk might be related to increased mucosal (urethra, bladder, peritoneum) absorption and prolonged exposure to a large volume of CHX solution when compared with skin surface disinfection, in which absorption is poor (Table 2). Tolerance of CHX in mouthwashes does not preclude anaphylaxis following more intense exposure during surgery, particularly through broken skin or mucosa [7]. However, CHX is frequently not thought of as the trigger for anaphylaxis, and the diagnosis is easy to miss. It is not administered by the anaesthetist, and its use is not documented. Multiple sources of exposure (eg, central venous catheter [CVC], urinary catheter, skin preparation) might cause anaphylaxis some time into surgery, even in recovery, and may not coincide with administration of the anaesthetics [9]. Retrospectively, however, in some patients, mild CHX-induced reactions precede anaphylaxis on subsequent exposure (up to 83% of patients in one case series) [5].

Although not comprehensive, epidemiologic data suggest that the number of cases of CHX allergy appears to be increasing, and its ubiquitous use is likely to increase allergy further (Table 1) [4]. Again, in a parallel to LA, attempts at identifying populations at risk have revealed sensitisation in cohorts that are regularly exposed: health care workers (HCWs), patients with leg ulcers or eczema, and those undergoing recurrent surgical interventions (Table 2). In Europe, 0.4–5.4% cases of contact dermatitis are due to CHX [3,7,10]. Seven percent of HCWs in Japan suffer from CHX-allergic contact dermatitis, but none of Danish HCWs do [7]. It is not clear whether type IV hypersensitivity predisposes to type I allergy.

Commercial availability of the CHX sIgE assay (commonly known as RAST) facilitates the diagnosis. In a

Table 1 – Chlorhexidine-containing products [4,5,8–10]

Antiseptic: mouthwashes (average 0.2%), sore throat lozenges/sprays, creams, toothpastes, wipes, powders, dressings
Eczema and acne creams/ointments/face washes
Skin washes/cleansers
Topical disinfectants
Suppositories
Preservative in eye drops, nasal sprays, and contact lens solutions and some sun creams
Dental implants
Urology/surgery: bladder washouts (up to 4% chlorhexidine), gels for catheterisation (Instillagel [®]), central venous catheters, 0.05–4% skin preparation/wash including “swab sticks”

Table 2 – Risk factors for chlorhexidine allergy or sensitivity [4,7,9] *

Sex/age	Nonatopic, middle-aged male
Risk factors	Previous mild allergic reaction to CHX (often overlooked) Recurrent surgical interventions (urologic and abdominal surgery in particular) Leg ulcers Health care workers
Exposure during	Urinary catheterisation Cystoscopy Central venous catheter insertion Cannulation Skin preparation

CHX = chlorhexidine.

* Medical products often lack clear CHX warning (compared with latex).

small study, immediate-onset occupational allergy was confirmed by skin prick testing and sIgE in 28% of HCWs reporting symptoms on exposure to CHX [11]. Recent studies confirmed that 5% of cases of intraoperative anaphylaxis in the United Kingdom and as many as 10% in Denmark are caused by CHX [4,9].

If CHX allergy is suspected, a referral to a drug allergy centre is necessary. A mast cell tryptase level should be measured immediately and at 2 and 24 h after the reaction. Raised levels that return to a normal baseline after 24 h confirm mast cell degranulation and IgE-mediated allergy. Normal levels do not rule out anaphylaxis completely, as it might be due to different pathogenetic mechanisms [5]. Diagnostic tests used to confirm allergy include skin prick/intradermal tests, sIgE, and, in doubtful cases, provocation testing. CHX sIgE levels decline over time, and the referral should be made within 6 mo of the reaction [8]. According to the British anaphylaxis guidelines, the anaesthetist involved in the case must refer the patient with intraoperative anaphylaxis. In other circumstances, the responsibility rests with the surgeon, urologist, or attending physician [5].

Japan banned CHX use on mucosal surfaces in 1984, and a US FDA warning followed in 1998 [4,5]. In the United Kingdom, a Medical Device Alert was issued in 2012 emphasising the risk of anaphylaxis to CHX [4]. However, when considering measures to prevent adverse reactions, it needs to be borne in mind that all antiseptics can cause allergic reactions in susceptible individuals. A complete ban of CHX may not be the best or only way forward. Instead, we suggest a multitiered approach. CHX-allergic individuals with confirmed CHX allergy must use alternative antiseptics (eg, povidone-iodine, ethanol) and must avoid products shown in Table 1. Hospitals need be prepared for the increase in incidence of CHX allergy and must have appropriate protocols in place. A multidisciplinary approach (allergist, anaesthetist, surgeon, urologist, theatre coordinator) and “free from CHX” packs with non-CHX-containing lubricants, CVC, and skin preparation should be introduced to allow for safe surgery for these patients.

Education of the medical and surgical community is needed to raise awareness of this increasingly common but often missed cause of anaphylaxis and allergy. Finally, a question arises of whether patients with previous mild reactions should be screened for CHX allergy using skin and blood tests.

Conflicts of interest: The authors have nothing to disclose.

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