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doi:10.1093/bja/aep247

### Four cases of anaphylaxis to chlorhexidine impregnated central venous catheters: a case cluster or the tip of the iceberg?

Editor—We describe four cases of anaphylaxis caused by chlorhexidine in patients undergoing anaesthesia for cardiothoracic procedures in our Trust over a 12 month period. In all of these cases, anaphylaxis was preceded by insertion of a central venous catheter (CVC) impregnated with silver sulphadiazine and chlorhexidine (ARROWgard Blue®). All patients received standard anaphylaxis management including the administration of i.v. epinephrine, steroids, and antihistamines. In each patient, a tryptase increase from baseline was demonstrated in the early post-reaction sample, indicating mast cell degranulation and confirming the clinical impression of anaphylaxis. Allergen-specific IgE testing (ImmunoCAP®) to chlorhexidine was also positive in all cases.

The first patient experienced two separate episodes of chlorhexidine-associated anaphylaxis. He had his initial procedure abandoned after developing anaphylaxis. An ARROWgard Blue® CVC was inserted immediately before his reaction, but the significance was not noted at the time. After investigation under the allergy team, he was found to be positive to chlorhexidine by specific IgE. His surgery was rescheduled and in light of his previous episode, all antiseptic preparations containing chlorhexidine were removed from the theatre. He had a second anaphylactic reaction after insertion of a second ARROWgard Blue® CVC. The external sterile set packaging did not carry a chlorhexidine warning label as it had been processed in a sterile services unit. The warning label on the central line packaging was noted after close inspection after the second reaction. After this case, the Trust has introduced clear chlorhexidine warning labels on the outer

packaging of the CVC packs in order to reduce the risk further of episodes of inadvertent exposure.

The second patient also developed anaphylaxis within seconds of insertion of an ARROWgard Blue® CVC. It was changed to a non-coated line intraoperatively. Owing to airway oedema, the patient was kept intubated for 2 days on the cardiac intensive care unit. After confirmation of chlorhexidine anaphylaxis, it was noted that he was receiving unprescribed 'Corsodyl' mouthwashes (containing chlorhexidine) on a regular basis. After stopping the mouthwashes, his airway swelling subsided and he was extubated without incident. The third patient was listed for a coronary artery bypass graft. Soon after insertion of an identical CVC line, he also developed cardiovascular collapse requiring high-dose vasopressors. We are currently investigating a fourth patient who has had anaphylaxis in the same setting as the previous patients (raised tryptase after insertion of a chlorhexidine-coated central line and positive IgE antibodies to chlorhexidine). It was specifically noted that in all four cases, bronchospasm was not clinically evident.

Chlorhexidine is a chlorophenyl biguanido antiseptic with two identical epitopes. This type of chemical conformation is known to be capable of cross-linking IgE antibodies on the surface of mast cells and basophils, subsequently causing histamine release in sensitized individuals in a manner similar to succinylcholine. Sensitization to chlorhexidine is undoubtedly through exposure, although this does not appear to be more common in health-care professionals who work in an environment where chlorhexidine is ubiquitous.<sup>1</sup>

First reports of anaphylaxis to this substance appeared in medical literature 25 yr ago<sup>2</sup> and subsequent reports have been published sporadically since, mainly involving reactions from topical applications to skin and mucous membranes (ophthalmic wash, urinary catheterization, rectal examination, and intranasal administration).<sup>3–7</sup> The severity of these cases prompted the Food and Drug Administration (FDA) in 1998, to issue an alert to the medical community about the potential for serious hypersensitivity reactions to chlorhexidine-impregnated medical devices.<sup>8</sup>

The incidence of chlorhexidine anaphylaxis is likely to be vastly under-represented; in a world-wide review in 2004, there were only 50 reported cases over a 10 yr period.<sup>9</sup> In response to our recent cases, the Immunology Department in Southampton is currently undertaking a historical review of patients who have had an episode of intraoperative allergy. They have so far discovered 19 patients with positive chlorhexidine 'ImmunoCAP' tests in Wessex out of 86 cases tested in the last 36 months. Of the 86 patients tested, 16 were anaesthetic referrals and of these seven tested positive for chlorhexidine 'ImmunoCAP'.

Anaphylaxis to chlorhexidine impregnated CVCs has been reported<sup>10</sup> previously. In our hospital, we have had four cases in the last 12 months. The incidence is likely to be much more common than previously thought and a high index of suspicion must be maintained by

anaesthetists who are faced with cases of intraoperative anaphylaxis.

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doi:10.1093/bja/aep248

## Ehlers–Danlos syndrome type IV in a child admitted in emergency with peritonitis

**Editor**—The diagnosis of Ehlers–Danlos syndrome (EDS) of type IV is rare in children. A 7-yr-old child was admitted to our hospital with septic shock and peritonitis. Emergency laparotomy found spontaneous perforation of the colorectal junction with bleeding and serious disruption on manipulation. Several biopsies were taken. The child's progress was marked by a thrombosis in the inferior vena cava inferior on a central venous catheter and re-appearance of peritonitis 10 days later. Laparotomy revealed large amounts of intraperitoneal blood with multiple haematomas

along the colon and diffuse bleeding. Haemorrhage was treated with plasma and platelets. EDS type IV was suspected and genetic assessment was sought. The diagnosis was confirmed by colonic biopsies, molecular biology which showed a heterozygous mutation of the COL3A1 gene, and fibroblastic culture of the skin. The family investigation was negative. One year later, the child has had a total colectomy with ileorectal anastomosis.

The incidence of EDS is 1:5000 births<sup>1</sup> and type IV represents 3–5% of the cases.<sup>2</sup> It is a genetic abnormality affecting the collagen metabolism, of autosomal dominant trait, although a significant percentage of mutations are sporadic<sup>3</sup> as in this case. Only 14 cases of spontaneous colonic perforation have been reported in the literature, but only two in children <10 yr of age.<sup>1 2</sup> Skin and joint manifestations are less prominent than in other types of EDS, and type IV presents with complications such as arterial, visceral, or colonic rupture, as in our patient.

In retrospect, this child had several major criteria of EDS:<sup>4</sup> history of spontaneous colonic perforation, easy bruising, characteristic face, keloid on the chin and forehead,<sup>3</sup> and translucent dry skin with venous prominence at thoracic area, thin fingers, and joint hyper mobility.<sup>5</sup> The coagulation disorders associated with the type IV EDS are related to platelet abnormalities, or deficiency in factors VIII, XI, or XIII,<sup>6 7</sup> but tests of haemostasis are often normal. The major abnormality of coagulation in EDS type IV is decreased vascular wall reactivity which prevents slowing of the microcirculation and the accumulation of platelets needed for the formation of thrombus and haemostasis.<sup>8</sup> There are no reports of thrombosis associated with EDS in the literature, but those observed in our patient may be related to the presence of the central venous catheter.<sup>9</sup>

The median survival with EDS is around 48 yr because of vascular or gastrointestinal complications.<sup>5</sup> Perioperative management should avoid triggers, such as raised arterial pressure, that can lead to vascular or gastrointestinal perforations. The long-term administration of  $\beta$ -adrenergic blockers has been proposed.<sup>2 10</sup> The use of non-steroidal anti-inflammatory agents may increase the risk of bleeding. Any invasive surgical procedures must be performed with great care. The surgeons chose a total colectomy because recurrent perforation is frequent in patients treated with resection and diversion.<sup>11</sup>

The association of 'spontaneous' colonic perforation, haemostatic disorders with tendency to easy bruise should raise a suspicion of a vascular type EDS. Early diagnosis will facilitate and improve the perioperative management.

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