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Perioperative anaphylaxis: Management and risk reduction strategies in 2024

Abstract

The Australian and New Zealand College of Anaesthetists (ANZCA) reports anaphylaxis is the most common cause of death associated with anaesthesia in Australia, and the incidence is rising. Anaphylaxis is a life-threatening event that without early recognition and prompt crisis management results in morbidity and mortality. Trigger agents for anaphylaxis in the Australian perioperative environment are commonly neuromuscular blocking agents, antibiotics and chlorhexidine. Many cases of mild to life threatening anaphylaxis (grades 1–3) in Australia are under-reported.

The Australian Perioperative Anaphylaxis guidelines have recently been updated to optimise management of patients experiencing anaphylaxis during anaesthesia. The Australian Therapeutic Goods Administration (TGA) also launched an initiative in March 2023 to reduce perioperative anaphylaxis, withdrawing 44 products containing pholcodine due to its association with anaphylactic reactions during general anaesthesia.

Keywords: perioperative anaphylaxis, trigger agents, grades of anaphylaxis, crisis management, anaphylaxis box, risk reduction strategies, pholcodine, chlorhexidine

Introduction

Anaphylaxis is a life-threatening event; without early recognition and prompt crisis management anaphylaxis may result in patient morbidity and mortality[1–3]. In the United Kingdom, incidence of perioperative anaphylaxis is estimated at one in every 7000 to 10 000 anaesthetics delivered[1]. While the Australian and New Zealand College of Anaesthetists (ANZCA) similarly provides statistics that anaesthesia is very safe, perioperative anaphylaxis is the most common cause of death associated with anaesthesia in Australia[2].

The ANZCA Safety of Anaesthesia report for 2015–2017 identified 35 deaths under anaesthesia; eight of these deaths (23%) were attributed to anaphylaxis[2]. The Victorian Consultative Council on Anaesthetic Mortality and Morbidity (VCCAMM) triennial report from 2012–2014 highlighted 227 cases of morbidity during anaesthesia; the primary cause of 54 events was anaphylaxis, including six deaths[3]. Harper et al.[1] and Gibbs et al.[4] both highlighted that not all cases of perioperative anaphylaxis are reported unless there is mortality, and the overall incidence of anaphylaxis in perioperative settings is rising. It is suspected that some cases of mild to life threatening anaphylaxis (grades 1–3) in Australia are not reported as reporting of cases where no mortality occurs is voluntary[1,4,5]. Under-reporting of anaphylaxis cases is hypothesised to be due to less severe clinical manifestations during surgery and anaesthesia, differential diagnoses and altered expression of symptoms[1,4,5].

This paper provides an overview of the recent changes in the prevention

and management of anaphylaxis in patients undergoing anaesthesia or surgery in the perioperative setting and the required nursing care to reduce and prevent the associated mortality and morbidity.

Background

The VCCAMM triennial report 2012–2014 highlighted trigger agents for cases of anaphylaxis in the operating theatre. Neuromuscular blocking agents (NMBAs) were the responsible trigger agents for 23 of 54 anaphylaxis cases identified[3]. Other known trigger agents included cefazolin, ticarcillin-clavulanic acid, ceftriaxone, chlorhexidine, patent blue V, hyaluronidase and gelofusine[3].

After publication of the VCCAMM report in 2015, recommendations were made to the Therapeutic Goods Administration (TGA) in Australia to review evidence that pholcodine was increasing sensitivity of patients to quaternary ammonium ions (QAI) in NMBAs[2,6,7]. Pholcodine is an opioid cough suppressant found in many cough medicines that can be purchased over the counter in Australia[7,8]. The QAIs in NMBAs act as an epitope that bind to immunoglobulin E (IgE) antibodies and generate anaphylactic responses. International researchers have recognised that previous exposure to QAI epitopes, in substances such as pholcodine, cleaning agents and topical cosmetics, can sensitise people to other medications with similar QAI epitopes resulting in anaphylaxis[4,9,10]. Florvaag et al.[11] and de Pater et al.[12] performed serum analysis of patients in Norway and found extensive evidence of reduced prevalence of IgE antibodies to NMBAs and episodes of perioperative anaphylaxis after the withdrawal of pholcodine from the Norwegian market[11,12].

The Australian TGA withdrew 44 products containing pholcodine from Australian pharmacies in March 2023 and initiated recalls on products with an associated risk of anaphylactic reactions during general anaesthesia[13,14]. In total, 55 products containing pholcodine have been cancelled from the Australian Register of Therapeutic Goods[14]. ANZCA supports the decision to withdraw pholcodine from the Australian pharmaceutical market and had approached the TGA to restrict inclusion of pholcodine in cough medicines with the aim of reducing incidences of anaphylaxis associated with NMBAs during general anaesthesia, similar to experiences overseas[2,3,7,15]. Patients consuming pholcodine in the 12–24 months prior to administration of an NMBA increase the risk of anaphylaxis during general anaesthesia. Vigilance in checking pholcodine consumption needs to be continued as there is the potential for people to have access to medicines that are restricted or withdrawn from market[5,7].

Table 1: Perioperative anaphylaxis grades of severity

Grade of severity	Clinical signs and symptoms
Grade 1 (mild)	Patients present with mucocutaneous clinical symptoms, such as urticaria, erythema and peripheral angioedema which are often not readily evident due to the sterile drapes covering patients during surgery[2,17].
Grade 2 (moderate)	Patients present with hypotension and/or bronchospasm combined with mucocutaneous clinical symptoms[2,17]. Hypotension and bronchospasm commonly occur during induction of anaesthesia, consequently these symptoms may be attributed to other causes[2,17].
Grade 3 (life-threatening)	Patients present with severe hypotension and bronchospasm, ventilation and oxygenation are compromised, with tachycardia and decreased tissue perfusion evident and 30% of cases have a reduced or absent capnography trace[2,17]. Decreased tissue perfusion associated with distributive shock may delay mucocutaneous symptoms of anaphylaxis until blood pressure levels are normalised[1,2,17].
Grade 4 (cardiac arrest)	Patients suffer cardiac or respiratory arrest. Pulseless electrical activity (PEA) is the most common presenting symptom of grade 4 anaphylaxis and is often preceded by bradycardia[2,17].

Discussion

Severity of anaphylaxis

Currently, the Ring and Messmer grading system, which was first described in 1977, is used by ANZCA and the Australian and New Zealand Anaesthetic Allergy Group (ANZAAG) to describe the clinical severity of anaphylaxis[2,16,17]. This grading system is summarised in Table 1.

Anaphylaxis presentations may be immediate or delayed. In the perioperative environment, common trigger agents for anaphylaxis are administered intravenously with onset of significant reactions occurring within three to five minutes of administration[1,2]. For example, anaphylaxis related to chlorhexidine is increasing[18,19]. When patients have a central venous catheter (CVC) impregnated with chlorhexidine inserted, the onset of anaphylactic reaction can be within three to five minutes[1]. However, chlorhexidine applied as skin preparation, wipes, swabs, eye drops, bladder irrigation, mouth washes, oral pastes or lubricant gel require cutaneous absorption and subsequent reaction times are slower (longer than 45 minutes) [1,18,19]. These delayed reactions are classed as mild to moderate (grades 1 or 2); they are not as severe and have less potential for morbidity and mortality[1].

Updates to management of anaphylaxis in the operating theatre

ANZCA and ANZAAG updated the Perioperative Anaphylaxis guidelines in 2022 as part of a five-yearly routine review. Recent changes to significant international guidelines have been made by other peak bodies, for example, the Association of Anaesthetists of Great Britain and Ireland (AAGBI), the Japanese Society of Anesthesiologists and the Brazilian Association of Allergy and Immunology[2,20].

Five key changes to the ANZCA 2022 guidelines are:

1. Cardiac compressions should be initiated at a systolic blood pressure of less than 50mmHg in the anaesthetised patient[2, p.2.]
2. A graded approach to volume replacement with an initial crystalloid fluid bolus of 500mL in a moderate (Grade 2) and 1000mL in a life threatening (Grade 3) reaction to be repeated as required and titrated to clinical response. In the case of a cardiac arrest (Grade 4) reaction the recommendation remains for an initial bolus of 2000mL[2, p.2].
3. A more graded approach to IV adrenaline bolus dosing with lower starting doses for each grade of reaction and guidance on how to escalate doses if there is no response[2, p.2].
4. Manual left uterine displacement (LUD) should be applied during the management of hypotension or cardiac arrest due to anaphylaxis in the pregnant patient to minimise aortocaval compression (in preference to left lateral tilt)[2, p.2].
5. Oesophageal intubation has been added to the differential diagnosis list for refractory bronchospasm and has been included on the immediate management card[2, p.3].

Management of grade 3 and grade 4 anaphylaxis in the operating theatre

ANZCA and ANZAAG developed reference cards for immediate and refractory management of anaphylaxis. The cards provide clarity for the perioperative team in managing individual patient experiences of anaphylaxis[2,20,21]. Anaphylaxis algorithms provided by ANZCA align with the Australian Resuscitation Council advanced life support algorithms to optimally manage a patient experiencing life-threatening anaphylaxis[2,20]. The differential diagnosis card assists with excluding other potential causes of PEA arrest and optimising crisis management of patients requiring resuscitation[2,20].

Adrenaline administration is emphasised to manage anaphylaxis as it reduces the pathophysiological effects of anaphylaxis[2,17,20,21]. Adrenaline increases cardiac output and promotes bronchodilation and vasoconstriction, reducing both mucosal oedema and mediator release[2,17,20]. Grades 3 and 4 anaphylaxis may require administration of adrenaline 1mg every two minutes or an adrenaline infusion to optimise blood pressure and ventilation[2,17,20]. Cases of lethal anaphylaxis have highlighted inadequate or delayed adrenaline administration[5].

Removal of possible trigger agents such as chlorhexidine, should be considered as refractory anaphylaxis can be due to continued exposure to the allergen. NMBAs and antibiotics, the most common allergens, should be discontinued if possible[2,5]. Between one and twenty per cent of perioperative anaphylaxis cases are biphasic, (secondary reactions occur), requiring crisis and or cardiac arrest management for a prolonged period of time and vigilance in patient monitoring[2,5].

Development of an anaphylaxis box

ANZCA and ANZAAG recommend each operating theatre has an anaphylaxis box on their resuscitation trolley for effective crisis management of anaphylaxis[2,20,21]. Cognitive

aids cards provide prompts and information to prioritise patient care in resuscitation[2,20,21]. A list of all products containing chlorhexidine and latex in each operating theatre is useful to identify potential triggers[18,19,22]. Supplements 1 and 2 include links to anaphylaxis reference cards and recommended inclusions for an anaphylaxis box.

Anaphylaxis risk reduction strategies

Pre-admission checklists for elective surgery should highlight patient history taking and documentation of allergies and sensitivities to inform perioperative staff of potential patient allergens[22]. Patients attending pre-admission clinics or who identify as sensitive to antibiotics, NMBAs, cleaning agents, cosmetics and chlorhexidine require allergen testing to confirm allergy status prior to elective surgery. Questioning about allergies should discuss development of skin rashes after insertion of intravenous cannula or application of antiseptic solutions, cosmetics or cleaning agents to skin, and development of oral swelling after use of mouthwashes[18,19,22]. Preventative strategies should be considered for all elective surgery patients who have previously experienced anaphylaxis[22]. An overview of anaphylaxis preventative strategies is provided in Table 2.

Adherence to the Australian College of Perioperative Nurses (ACORN) Latex and chlorhexidine sensitivity standard reduces risk of patient anaphylaxis to latex and chlorhexidine[22]. This standard highlights the need for training perioperative personnel to recognise latex and chlorhexidine sensitivity, and the importance of latex-free perioperative areas as well as identifying steps to be taken to reduce latex and chlorhexidine exposure in the perioperative environment[22].

Anaphylaxis box (closed)
Source: Monash Children's Hospital

Anaphylaxis box (open, showing contents)
Source: Monash Children's Hospital

Having a list of products containing chlorhexidine and latex in the anaphylaxis box helps to identify potential patient exposure to chlorhexidine and latex[2,22]. Common chlorhexidine-containing products which induce anaphylaxis are urinary catheter lubricant, CVCs coated in chlorhexidine and topical solutions[18,19,22]. Alternative chlorhexidine-free products should be available in every operating theatre for use with patients who have known sensitivities[18,19,22].

Sensitisation to chlorhexidine increases with repeated exposure, particularly with exposure to higher concentrations of chlorhexidine[18,19]. Solutions with 2–4% chlorhexidine are irritating to the epidermis, damaging this skin barrier and increasing the risk of chlorhexidine sensitisation[18,19]. The benefits of using 2-4% chlorhexidine solutions to reduce microbial populations during skin disinfection lacks clarity and evidence[18,19,22].

Patient follow-up and investigation after crisis management is essential to ensure triggers are found and to reduce the risk of greater sensitisation to triggers[2,23]. Patients who experience perioperative

Table 2: Anaphylaxis preventative strategies

Preventative strategy	Actions
Pre-admission checklists	A thorough history is taken with clear documentation of: • allergies and sensitivities on medication charts and surgical safety checklist. Patients are questioned about: • sensitivities to antibiotics, NMBAs, cleaning agents and cosmetics • allergies and development of skin rashes after application of antiseptic solutions to skin and insertion of intravenous cannula, or development of oral swelling after use of mouthwashes • consumption of cough suppressants. After patient attendance at pre-admission clinic, communication with the operating theatre about patient allergies is completed prior to day of surgery admission.
Allergy testing prior to elective surgery	Patients who have previously experienced a known anaphylactic reaction (grades 1–4) are allergy tested prior to undergoing elective surgery to confirm allergen.
Lists of products containing latex and chlorhexidine	A list of products containing latex or chlorhexidine is available in each operating theatre and in each anaphylaxis box to enable rapid removal of allergens, when required.
Alternative products available	Alternative products, without latex and chlorhexidine, are available, including CVCs, IDCs, tourniquets, face masks, tapes, gloves, antiseptic solutions, dressings and lubricants.
Red alert bracelets	Red alert bracelets are applied to patient wrists or legs to highlight patient allergies and reactions to allergen exposure.
Surgical safety checklist	Documentation is completed early to enable preparation of the operating theatre, holding bay and PACU for patient arrival and care.

anaphylaxis must be informed of the event and given referrals for follow-up – letters and brochures from the anaphylaxis box can be completed and placed in their history for discussion when the patient is able to understand the implications of the event[2,21,23].

Perioperative nurses attending multi-disciplinary crisis management training optimises teamwork and familiarity with anaphylaxis guidelines and reduces patient morbidity and mortality during clinical anaphylaxis crises[2,24]. Allocation of a nursing staff member to an anaphylaxis portfolio can provide all perioperative staff with ongoing updates to anaphylaxis preventative measures and management[21]. The staff member can ensure all anaphylaxis protocols are kept up to date and are followed in the operating theatre.

Conclusion

In Australia, perioperative anaphylaxis is an infrequent complication of anaesthesia but is often associated with morbidity and mortality. Early recognition of anaphylaxis and effective crisis management by anaesthetists and the perioperative team is associated with best patient outcomes. Access to an anaphylaxis box facilitates crisis management of a patient experiencing anaphylaxis and assists with identification of trigger agents. Patient referral to allergy clinics is essential after the event to identify trigger agents and minimise future anaphylaxis episodes that can be more severe. Risk reduction strategies should be employed in all perioperative environments to identify patients who are at high risk of anaphylaxis and to remove trigger agents prior to commencement of their perioperative journey.

Declaration of conflicting interests

The author has declared no competing interests with respect to the research, authorship and publication of this articles.

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Supplement 1: ANZCA and ANZAAG reference cards

Reference card	Available from
Anaphylaxis during anaesthesia – immediate management (Paediatric)	www.anzca.edu.au/resources/professional-documents/endorsed-guidelines/anaphylaxis-card-2-paediatric-immediate-management.pdf
Anaphylaxis during anaesthesia – immediate management (Adult)	www.anzca.edu.au/resources/professional-documents/endorsed-guidelines/anaphylaxis-card-1-adult-immediate-management-2022.pdf
Anaphylaxis during anaesthesia – refractory management chart (Paediatric)	www.anzca.edu.au/resources/professional-documents/endorsed-guidelines/anaphylaxis-card-4-paediatric-refractory-managemen.pdf
Anaphylaxis during anaesthesia – refractory management chart (Adult)	www.anzca.edu.au/resources/professional-documents/endorsed-guidelines/anaphylaxis-card-3-adult-refractory-management-202.pdf
Differential diagnosis card for anaphylaxis box	www.anzca.edu.au/resources/professional-documents/endorsed-guidelines/anaphylaxis-card-5-differential-diagnosis-2022.pdf
Post crisis management	www.anzca.edu.au/resources/professional-documents/endorsed-guidelines/anaphylaxis-card-6-post-crisis-management-2022.pdf

Supplement 2: Recommended contents of anaphylaxis box

Recommended number	Item	Notes
6 cards in total	Cognitive aid cards: • Anaphylaxis during anaesthesia – immediate management (Paediatric) • Anaphylaxis during anaesthesia – immediate management (Adult) • Anaphylaxis during anaesthesia – refractory management chart (Paediatric) • Anaphylaxis during anaesthesia – refractory management chart (Adult) • Differential diagnosis card for anaphylaxis box • Post crisis management.	To assist the perioperative team and provide clarity in managing individual patient experiences of anaphylaxis.
4 of each	Pathology request forms, plain serum pathology tubes for tryptase specimens in pathology bags.	For follow-up investigation and identification of allergens.
1 of each	Instructions for drug infusion preparation – adrenaline, noradrenaline, vasopressin and salbutamol.	Optimises preparation speed of vasoactive infusions, particularly for staff not familiar with these infusions.
2 of each	Patient form letters and information brochures that provide details about reactions and treatment individual patients received during their anaphylaxis episode and include recommendations for follow-up to investigate potential triggers of the anaphylaxis.	These can be included in the patient's history for discussion when the patient is able to understand the implications of the event.
2 of each	ANZAAG referral forms.	These begin the process of investigation for trigger agents under safe conditions.
1 of each	List of all products containing chlorhexidine and latex in each operating theatre.	This is useful to identify patient exposure to chlorhexidine and latex.