Anaphylaxis update

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There have been a number of developments in the field of perioperative anaphylaxis over the last few years. I am going to focus on 3 main areas: perioperative anaphylaxis management guidelines, cefazolin anaphylaxis and sugammadex anaphylaxis.

ANZCA/ANZAAG Perioperative anaphylaxis management guidelines

These guidelines and management cards were originally developed by ANZAAG and endorsed by ANZCA in 2013. The first revision in 2016 was co badged by ANZAAG and ANZCA. The second revision was completed this year and is now out as a pilot.

The key changes in the 2022 guideline are:

- Cardiac compressions should be initiated at a systolic blood pressure of less than 50mmHg in the anaesthetised patient.
- 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.
- 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.
- 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).
- Oesophageal intubation has been added to the differential diagnosis list for refractory bronchospasm and has been included on the immediate management card
- Some changes have been made to the layout and colour scheme of the cards

Cefazolin anaphylaxis

Cefazolin is one of the 3 main causes of perioperative anaphylactic reactions in New Zealand and Australia (along with neuromuscular blocking drugs and chlorhexidine). Historically it has been thought that there was a significant risk (up to 10%) of cross sensitivity between penicillins and cephalosporins due to the shared beta lactam ring and the advice given to patients who had an anaphylactic reaction to any of these drugs was to avoid all beta lactam antibiotics. In the context of surgical antimicrobial prophylaxis vancomycin and clindamycin use was (and still often is) recommended in these patients.

Over time it has become evident that the patterns of cross sensitivity between penicillins and cephalosporins and between different cephalosporins are variable and that many patients who are allergic to one drug in the group are able to tolerate others. One of the strong predictors of cross sensitivity is the presence of common side chains. Cefazolin has a unique R1 side chain. This means that **patients with a history of IgE mediated immediate hypersensitivity reactions to cefazolin are at low risk of reacting to penicillins or other cephalosporins and should be given these drugs if required.** The surgical antimicrobial prophylaxis guidelines at ADHB have been changed accordingly. Cefuroxime is now the recommended antibiotic in patients with cefazolin anaphylaxis. Cefazolin is the recommended antibiotic in patients with anaphylaxis to penicillin or another cephalosporin.

The unnecessary restriction of antibiotic usage due to unfounded concerns about cross sensitivity and

allergy result in increased healthcare costs, increased morbidity and increased mortality for patients. It is important to distinguish between **immediate** hypersensitivity reactions/IgE mediated reactions/anaphylaxis and **delayed** hypersensitivity reactions. The mechanisms underlying delayed hypersensitivity reactions are poorly understood. Red flags on history include mucosal ulceration (mouth, eye or genitals) and desquamating skin lesions. **Any patient with a severe cutaneous adverse reaction to penicillin should not be given any beta lactam antibiotics** and should be referred to immunology for further assessment. Alternative antibiotic prophylaxis outside of the class should be used i.e. gentamicin, clindamycin or vancomycin.

Sugammadex anaphylaxis

Sugammadex is a medication which is increasingly being used for reversal of neuromuscular blockade as an alternative to neostigmine. Sugammadex was approved for use in Europe, Australia and New Zealand in 2008. It was approved for use in Japan in 2010. It was not approved by the FDA until 2015 due to concerns about hypersensitivity reactions. Currently over 90% of reversal agent used in Japan is sugammadex. At ADHB neostigmine is still our main reversal agent but our sugammadex usage (based on number of 200mg vials dispensed) has increased tenfold between 2015 and 2021 (354 vials in 2015 to 3610 vials in 2021).

Sugammadex is a modified gamma cyclodextrin which antagonises aminosteroid neuromuscular blockers (rocuronium and vecuronium) by encapsulating the drug molecule in the plasma. Sugammadex has several clinical advantages compared to neostigmine but there are significant concerns regarding cost and potential to cause anaphylaxis.

At ADHB in 2021 the cost of a 200mg vial of sugammadex was $120 (minus an unknown rebate). The cost of a pre-mixed vial of neostigmine and glycopyrrolate was $2.09.

In Japan the estimated incidence of anaphylaxis to sugammadex, based on a number of large retrospective analyses, is between 1:2,500 and 1:5,000. This is similar to the quoted incidence of anaphylaxis to rocuronium and suxamethonium.

There are at least 2 mechanisms of anaphylaxis to sugammadex: (1) IgE mediated immediate hypersensitivity reactions with sensitisation due to previous use or exposure to similar molecules such as cyclodextrins in food additives and cosmetics in the community (2) Non IgE mediated, dose related hypersensitivity reactions.

There continue to be case reports claiming benefits temporally related to the administration of sugammadex in cases of rocuronium anaphylaxis. In all these cases conventional resuscitative therapies had also been administered. In vitro and in vivo human models of anaphylaxis have not been able to demonstrate immunologically mediated attenuation of established anaphylaxis. The observed therapeutic effect of sugammadex on resuscitation may be to increase muscle tone (and therefore, reduce venous capacitance) in circumstances where there is severe distributive shock and inadequate resuscitation. The resumption of spontaneous (negative pressure) ventilation after reversal of neuromuscular blockade may also increase venous return. There are potentially practical difficulties during resuscitation if neuromuscular blockade is reversed. The 2022 ANZCA/ANZAAG perioperative anaphylaxis management guideline does **not recommend the use of sugammadex in resuscitation of suspected anaphylaxis to rocuronium.**