Editorial

Perioperative anaphylaxis: progress, prevention and pholcodine policy

This issue of *Anaesthesia and Intensive Care* includes the publication of the second iteration of the Australian and New Zealand Anaesthetic Allergy Group (ANZAAG)/Australian and New Zealand College of Anaesthetists (ANZCA) Perioperative Anaphylaxis Management Guidelines. This second iteration was first launched at the ANZCA Annual Scientific Meeting in 2016. There is much to be celebrated here. These guidelines are a marked improvement on the original ANZAAG guidelines published in 2013, which were the first in the world to incorporate cognitive aids to assist with management of perioperative anaphylaxis.

The new guidelines are the culmination of efforts by a dedicated working group within ANZAAG to assess and improve upon the original resource. The second version includes redesigned adult and new paediatric management cards. Changes have been guided by testing in simulation settings and feedback from anaesthetists who have used the cognitive aids during the management of acute perioperative anaphylaxis. Attention has been directed to both the content and presentation of the information on the cards in order to optimise the performance of clinicians managing perioperative anaphylaxis. The recommendations have also been through a rigorous process resulting in the clinical guideline documents which have been co-badged with ANZCA.

Outcomes for patients exposed to the life-threatening risk of perioperative anaphylaxis can be improved by maintaining the very high standard of training of anaesthetists, combined with ongoing mandatory participation in continuing professional development (CPD) crisis management activities, including anaphylaxis. It is central to best management that anaesthetists are familiar with the use of the cognitive aids prior to use in a crisis. Early diagnosis and rapid deployment of algorithms as outlined in the ANZAAG guidelines are key factors in reducing morbidity and mortality.

Although the occurrence of anaphylaxis in association with anaesthesia might be deemed to be unavoidable, its incidence could (and should) be reduced by the pursuit of safer drugs. Data from recent anaesthesia mortality and morbidity reviews indicate that anaphylaxis is the most frequent cause of Category One deaths (cases where “it is reasonably certain” that the death was caused by anaesthesia or factors under the control of the anaesthetist). The recent report ‘Safety of Anaesthesia: a review of anaesthesia related mortality reporting in Australia and New Zealand 2009–2011’ identified 22 deaths in this category. Seven deaths were due to anaphylaxis and in four of these, the most likely trigger was a neuromuscular blocking agent (N MBA). This exceeded the deaths due to other causes such as airway-related deaths (5) and aspiration (4). This pattern continues with the mortality data currently being collated for the 2012–2014 Safety of Anaesthesia report (L. McNicol, personal communication): for this period, there were 23 Category One anaesthesia-related deaths, seven of which were definitely due to anaphylaxis with an additional unexplained cardiac arrest at induction in which anaphylaxis could not be excluded; all these cases involved NMBAs.

The hazard posed by perioperative anaphylaxis is also documented in the 2012–2014 Triennial Report of the Victorian Consultative Council on Anaesthetic Mortality and Morbidity (VCCAMM) (L. McNicol, personal communication). This Council reviews morbidity as well as mortality, and during this triennium, there were four deaths due to anaphylaxis (two suxamethonium, two rocuronium) and a total of 48 cases of anaphylaxis causing morbidity (L. McNicol, personal communication); of these, more than half (25 case reports) were due to the administration of NMBAs; there were 13 cases in which antibiotics were the trigger and 10 due to other adjuvant agents.

These alarming statistics demand that we not only consider how we best manage perioperative anaphylaxis when it occurs but also embrace ways in which the incidence can be reduced. There is evidence that we can take some action to potentially limit the number of cases of anaphylaxis caused by NMBAs. This would necessarily reduce the morbidity and mortality of anaesthesia in Australia and New Zealand.

The allergic portion of the N MBA molecule (epitope) is thought to be the tertiary or quaternary ammonium ion (QAI). The most common mechanism of anaphylaxis, mediated by IgE, involves the immune system being presented with an antigen and making antibodies to it. Thus the individual becomes sensitised and predisposed to anaphylaxis on subsequent exposure to the antigen. Interestingly, many patients proven to have anaphylaxis to N MBAs have their reaction during their first relaxant anaesthetic. So where are they getting their antibodies from?

Studies by Florvaag and Johansson indicated that there was a large difference in rates of anaphylaxis to NMBAs in Norway (high) and Sweden (low). They went into the homes of residents in both countries to identify sources of QAIs. The predominant difference identified was in the availability and
use of the over-the-counter cough suppressant pholcodine (PHO). PHO was not available in Sweden and was widely used in Norway. It was postulated that the substituted ammonium ion structure of PHO (see Figure 1) was resulting in sensitisation and an increased reaction rate to NMBAs observed in Norway relative to Sweden.

The subsequent ‘pholcodine hypothesis’ led to the voluntary withdrawal of the single PHO product on the market in Norway. A reduction in NMBA anaphylaxis was observed over three years subsequent to this action. A recent study looking at the situation a further three years on from the withdrawal showed that the significant reduction in IgE-sensitisation to suxamethonium (a QAI), and rates of anaphylaxis reporting observed three years after PHO withdrawal continued throughout this period. The authors noted that the relative risk of receiving a report of a possible anaphylaxis was reduced to 0.76 in the first three years following PHO withdrawal and further to 0.65 in the next three years. This falling trend had a P-value of <0.001. Moreover, no deaths attributed to NMBA anaphylaxis occurred in the final four years of the nine-year study period.

It is reasonable to ask why PHO has not been withdrawn from the Australasian market. PHO is most commonly sold in Australia for cough suppression and is a component of 55 medications available over the counter in Australia. Would withdrawal represent removal of a valuable therapeutic agent?

A review by the European Medicines Association (EMA) was undertaken in 2011 to consider possible removal of PHO from the European market. The EMA’s own review suggested “Being such an old product the methodology used in most efficacy studies with PHO would be considered poor by modern standards”. Most studies were not adequately controlled, either with active or placebo medications, and some were performed using combination products, which makes it difficult to isolate and measure the efficacy of the single component PHO. The largest study of efficacy of PHO conducted in the last 30 years had only 129 patients enrolled, no placebo arm and was funded by the industry.

A Cochrane study looking at over-the-counter cough medicines in 2012 concluded “there is no good evidence for or against the effectiveness of over-the-counter medicines in acute cough”.

The EMA review noted that the case for PHO being responsible for the development of antibodies that could react with NMBAs during anaesthesia and cause anaphylaxis was “biologically plausible”. It also noted that “cross sensitisation has also been observed in many countries where PHO is not on the market, suggesting that other substances may also trigger cross-sensitisation”. They advocated a “new post-marketing study investigating the possibility of an association between pholcodine and anaphylactic reactions to NMBAs should be carried out”.

Given that the review failed to find convincing evidence of PHO efficacy, yet found a plausible argument supporting the possibility of cross-sensitisation, the subsequent EMA conclusions were somewhat inconsistent. The EMA conclusion was that the “benefits of pholcodine-containing medicines continue to outweigh their risks” and declined a ban. This ruling ignores the principle that, in the absence of proven efficacy, the responsible approach is ‘first, do no harm’. They advocated waiting for further studies to provide proof of the association between PHO and NMBA anaphylaxis. Given the relative rarity of anaphylaxis such a trial would involve millions of patients and take many years. Meanwhile, people continue to ingest PHO, and may incur

Figure 1: Structures of pholcodine, rocuronium and suxamethonium, highlighting the common tertiary/quaternary ammonium epitopes.
morbidity or mortality as a result.

It is worth noting that there are cough medicines available on the market in Australia and New Zealand with alternative additives to PHO (such as dextromethorphan). Patients would still have the option of using an over-the-counter cough suppressant should they so desire.

In Australia and New Zealand, approaches by both ANZAAG and ANZCA to the relevant bodies (the Therapeutic Goods Administration [TGA] and Medsafe, respectively) regarding measures to protect consumers from the potential danger of PHO have had disappointing results to date. Despite absence of data supporting efficacy, both a complete ban or a change to prescription-only to restrict availability have been refused. Both bodies have cited the EMA decision and the lack of proof that PHO is responsible for an increased rate of NMBA anaphylaxis.

In Australia the argument is hampered by a lack of mandatory reporting of such serious reactions. The TGA in particular cited a lack of reported cases of anaphylaxis in Australia to show that there is not a significant problem with NMBA anaphylaxis in this country. Subsequently the results of the ANZCA Triennial Mortality Report^2^ and data from ANZAAG testing centres have been provided to the TGA. The internal ANZAAG survey (H. Crilly, personal communication) provided to the TGA found that there were 189 skin test–proven cases of anaphylaxis to NMBA in the time period 2009–2011, corresponding with the anaesthetic mortality report. These reports were gathered from 12 of the 21 centres known to specialise in testing patients after perioperative anaphylaxis during the relevant time period. Clearly, this represents an incomplete, yet significant, amount of morbidity and mortality.

The TGA also indicated that one of the reasons that they had been unwilling to withdraw PHO from the Australian market has been lack of correlation of rates of PHO antibodies with rates of PHO consumption. A recent study by Katelaris et al^1^ has provided new evidence that links PHO consumption with antibodies to PHO, morphine (MOR) and suxamethonium. It compared the IgE antibody levels in Australia, a relatively high consumer of PHO, with those in Japan and Korea, where PHO is not available. Specifically, it found that in Australia 9.6% were positive to PHO and 8.6% to MOR compared to 0.8% (PHO) and 0.8% (MOR) in Japan, and 1.0% (PHO) and 0.5% (MOR) in Korea. These authors concluded that this study supports the PHO hypothesis.

Data recently presented at the Australian Society of Clinical Immunology and Allergy (ASCIA) from Royal North Shore Hospital in Sydney, showed that 68% of skin test positive NMBA anaphylaxis patients had positive specific IgE antibodies (sIgEs) to PHO. When benzylisoquinoline NMBA reactors were excluded (benzylisoquinolines appear to have less affinity for these antibodies), 80.5% had sIgEs to PHO (cut-off 0.23 kUAI/l) (M. Rose, personal communication). This is further evidence that PHO could be playing a role in NMBA anaphylaxis.

We believe that allowing PHO to be freely available over the counter in Australia confers an unacceptable risk to consumers, with negligible benefit. The lack of scientific data supporting the efficacy of PHO has been acknowledged by both the TGA and the EMA in previous reviews. We continue to be concerned that the public are exposed to significant harm with no proven benefit from the continued widespread availability of over-the-counter preparations containing PHO.

By any measure, modern anaesthesia in Australia and New Zealand is safer than it has ever been. However, the target should be zero for primary anaesthesia mortality. It is timely to again raise the issue of possible harm related to the free availability of PHO with the drug regulation agencies in Australia and New Zealand. Without disadvantage to consumers, it seems very likely that the removal of PHO from cough mixtures or at the very least, restriction to prescription-only, could further reduce ‘preventable’ anaesthesia-related harm to Australasian patients.

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