

Anaphylaxis and anaesthesia – can treating a cough kill?

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In Australia, anaphylaxis during surgery has been estimated to occur in approximately 1 in 10 000 cases. The mortality rate is approximately 4%, with long-term brain injury in an additional 2% of cases.¹ Neuromuscular blocking drugs are responsible for approximately 60% of intraoperative anaphylaxis.² Anaphylaxis is twice as likely to occur during surgery when a muscle relaxant is used.³ The reported rates of anaphylaxis caused by neuromuscular blocking drugs are much higher in Australia and France³ than in some other countries.^{4,5} Unfortunately the true incidence of intraoperative anaphylaxis in Australia is unknown. Reporting is voluntary and complicated by the fact that multiple drugs are administered at the time of anaesthesia, making the cause of anaphylaxis unclear. The Therapeutic Goods Administration in Australia received 231 reports between January 2001 and December 2011 citing neuromuscular blocking drugs as a possible cause of anaphylaxis.⁶ However, a recent study from Western Australia reporting on the 10-year period 2002 to 2011, found 80 cases of life-threatening anaphylaxis in which neuromuscular blocking drugs were established as the cause of the reaction with subsequent testing.⁷ These data, derived

from a single state which contained a little over 10% of the Australian population in 2011⁸, suggests that anaphylaxis to neuromuscular blocking drugs is under-reported.

The quaternary ammonium ion in neuromuscular blocking drugs is the allergenic portion (epitope). It allows specific binding of immunoglobulin (IgE) to the drug,⁹ which can result in IgE-mediated anaphylaxis. However, in up to 50% of cases, anaphylaxis occurs on first exposure to a neuromuscular blocking drug.^{5,10} This suggests that there is an alternative source of sensitisation.

Anaphylaxis to neuromuscular blockers in Norway was observed to be approximately 10 times higher than in neighbouring Sweden.¹¹ An unknown environmental factor containing the quaternary ammonium ion was suspected to be responsible for the difference. Rates of exposure to 84 household chemicals and medicines were found to be similar with the exception of pholcodine, an opioid antitussive. In Norway up to 40% of the population was exposed to this cough mixture, but pholcodine was not available in Sweden.⁵ Approximately 6% of Norwegian blood donors had specific IgE antibodies to pholcodine, whereas in Sweden there were no sensitised individuals.¹²

Further studies showed that pholcodine consumption causes production of specific IgE against the quaternary ammonium ion. Without ongoing pholcodine consumption, antibody titres fall to low levels within two years. Re-exposure, however, has a profound booster effect and there is a dramatic rise in pholcodine antibodies in individuals with known previous sensitisation to pholcodine and suxamethonium.⁵ Pholcodine was subsequently withdrawn from the Norwegian market by the supplier. Three years after withdrawal, the rate of anaphylactic reactions to neuromuscular blocking drugs in Norway had significantly reduced.¹³

Pholcodine has been used as a cough suppressant since the 1950s. The evidence supporting its efficacy was reviewed by the European Medicines Agency (EMA) in 2011. It commented that 'Being an old product, the methodology used in most efficacy studies with pholcodine would be considered poor by modern standards.'¹⁴

The only efficacy study in the last 30 years had significant design flaws. It involved only

From the Editor



The misadventures of celebrities regularly highlight the growing problem of misuse of prescription drugs. Malcolm Dobbin reports that deaths involving prescription drugs now exceed those caused by car crashes.

When used appropriately, taking several prescription drugs together can be beneficial. Ruth Webster and Anushka Patel discuss the prospects for polypills in

preventing cardiovascular events.

Serious adverse events can result not only from prescription drugs, but also from over-the-counter medicines. Helen Crilly and Michael Rose explore the link between pholcodine cough mixtures and anaphylaxis during surgery. Jerome Sarris reminds us that even herbal medicines – such as those used for mental health – can interact with other drugs.

The prevalence of problem allergies appears to be increasing. It is therefore appropriate for William Smith to assess the role of allergen immunotherapy, including sublingual immunotherapy.

The diagnosis of diabetes is also increasing and Michael d'Emden proposes changing the diagnostic process. Measuring glycated haemoglobin (HbA1c) is a simpler method than the traditional oral glucose tolerance test.

129 patients randomised to receive pholcodine or dextromethorphan, with no placebo arm. Funding for the study came from a manufacturer of pholcodine. Although the conclusion was that 'the efficacy of a three-day course of pholcodine is similar to that of dextromethorphan in the treatment of adult patients with acute, non-productive cough',¹⁵ the EMA said this conclusion was 'non-validated and subjective'.¹⁴ The lack of a control group means that the patients may have had a spontaneous recovery from viral coughs.

A Cochrane review in 2012 of all randomised controlled studies comparing over-the-counter cough suppressant medicines (including dextromethorphan) with a placebo arm in adults and children affected by acute cough included 25 trials. It concluded that 'there is no good evidence for or against the effectiveness of over-the-counter medicines in acute cough'.¹⁶

So what are the implications of the pholcodine hypothesis for Australia? According to the Australian Register of Therapeutic Goods, pholcodine is found in 58 over-the-counter cough mixtures and lozenges.¹⁷ In Norway there was only one pholcodine-containing product.⁵ Any decision to remove or restrict availability of pholcodine in Australia will affect more products and have financial implications for the pharmaceutical industry. A decision to remove or restrict pholcodine must be carefully considered on merit alone, removing financial confounders and keeping the best interests of patients as the central focus.

The TGA has been advised of emerging evidence in this area. It has agreed with the decision of the EMA which concluded that 'the evidence of a link between pholcodine and neuromuscular blocking drug-related anaphylaxis is circumstantial, not entirely consistent and does not support the conclusion that there is a significant risk of cross-sensitisation to neuromuscular blocking drugs and subsequent development of anaphylaxis during surgery. Further data need to be generated to clarify the possibility of an association

between pholcodine use and neuromuscular blocking drug-related anaphylaxis'.¹⁴

The evidence linking pholcodine to anaphylaxis due to neuromuscular blocking drugs is compelling, but not yet perfect or complete. In particular, data matching pholcodine consumption and the incidence of reactions by country is hampered by a lack of mandatory reporting systems for anaphylactic reactions throughout the world. Data to establish proof would require a randomised controlled trial of millions of patients. Such a study would be prohibitively expensive. While it may be argued that there is insufficient proof to ban pholcodine, its lack of efficacy and a strong suspicion of danger should be regarded as sufficient for it to be withdrawn.

The adverse outcomes of anaesthetic anaphylaxis – brain injury, permanent disability and death – are significant for the individual and the community. There is good evidence and a plausible mechanism linking pholcodine to an increased risk of anaphylactic reactions to neuromuscular blocking drugs. If pholcodine was being evaluated as a new drug today it is likely that it would not be approved. Furthermore, there are alternative medicines which do not appear to have the same risk of serious harm.

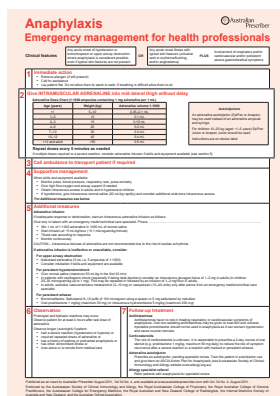
When the arguments are weighed, we believe the over-the-counter availability of products of unproven efficacy cannot be justified when pholcodine has been linked with such a serious complication as anaesthetic anaphylaxis and when alternative treatments exist. Discussions are ongoing with regulatory authorities in Australia and New Zealand. If it is not possible to withdraw pholcodine from the market, we propose a re-classification to 'prescription only'. This would allow medical practitioners to consider the risk of harm before prescribing pholcodine. ◀

Conflict of interest: none declared

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Letters to the Editor

Conflict of interest

Editor, – Given what we know about the effects of conflicts with the pharmaceutical industry and medical practice, it is simply no longer acceptable to have significant conflicts of interest and provide meaningful information on the benefits and harms of medicines, especially psychiatric medicines. There is a scholarly review of this issue by the co-founder of the Cochrane Collaboration and co-author of the CONSORT guidelines.¹

Some articles in *Australian Prescriber* are written by authors who have received payments from the pharmaceutical industry. Your publication – and NPS MedicineWise – risks losing its stature if it continues publishing reviews by extensively conflicted authors.

Robert Purssey
Psychiatrist
Brisbane

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The Editorial Executive Committee of Australian Prescriber comments:

The Editorial Executive Committee thanks Dr Purssey for raising the topic of conflict of interest. This topic is of particular importance to

organisations that produce independent drug information.¹

There are several ways that conflict of interest is dealt with in *Australian Prescriber*. All authors and referees are asked to declare any conflicts of interest. The members of the Editorial Committee also have to declare any conflicts of interest and they provide an annual statement of their interests to NPS MedicineWise, the publisher of *Australian Prescriber*.

The Editorial Committee does not automatically reject articles written by authors who declare a conflict of interest. Many clinicians have received support from the pharmaceutical industry to conduct clinical trials. While this may raise the risk of bias, the Editorial Committee believes this can be managed during the editorial process. All articles and editorials are peer-reviewed not only externally, but also by each member of the Editorial Committee. Usually extensive changes are made to articles submitted to *Australian Prescriber*. The Editorial Committee is confident that this process reduces the risk of the published version of a paper being biased by a conflict of interest.

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