Pholcodine consumption and general anaesthesia

Introduction

This statement has been prepared in response to the decision of the Australian Government Therapeutic Goods Administration (TGA) to withdraw pholcodine-containing products from the market. Evidence shows that pholcodine consumption in the 12-month period prior to a general anaesthetic may increase the likelihood of a patient developing anaphylaxis to a neuromuscular blocking agent (NMBA).

ANZCA welcomes the TGA's decision to withdraw pholcodine-containing products from the Australian market. The decision is expected to significantly reduce the incidence over time of anaphylaxis to NMBAs.

This paper provides a brief discussion of the issues and advice to anaesthetists.

Background

On 28 February 2023, the TGA issued a safety alert[1] advising of the recall of 44 pholcodine-containing products. The safety alert followed a review of the products by the TGA's Pharmacovigilance Risk Assessment Committee.

The Committee identified there was sufficient evidence to indicate that consumption of pholcodine in the 12-months prior to general anaesthesia puts patients at a higher risk of an anaphylactic reaction to NMBAs. Patients have been advised to identify whether they have consumed pholcodine-containing products and to advise their health practitioner of this prior to a general anaesthetic[1].

On 17 March 2023, the TGA reiterated the safety alert[2] about pholcodine use before general anaesthesia. Health professionals were reminded to check if patients have consumed pholcodine-containing products within the 12-months prior to a general anaesthetic and to remain aware of the risk of anaphylactic reactions in these patients.

Medsafe, in New Zealand, is still seeking expert advice about pholcodine consumption and currently lists pholcodine as a pharmacy-only product.

Concerns of anaesthetists

Following the advice from the TGA, anaesthetists may have concerns about:

- Using NMBAs
- Choosing which NMBA to use
- Proceeding with non-urgent surgery in the face of recent pholcodine consumption
- Asking their patients about pholcodine consumption.

NMBAs and pholcodine consumption

The decision to use NMBAs, and the choice of NMBA for a particular patient and clinical situation, is best decided by the treating anaesthetist. Anaphylaxis risk is only one factor that needs to be considered when determining both the appropriateness of NMBA use and the choice of NMBA. This risk must be balanced against the benefits of the use of NMBAs.

Pholcodine consumption is not the only risk factor for developing anaphylaxis to NMBAs. Previous NMBA exposure can result in sensitisation to NMBAs as may environmental agents other than pholcodine[3]. Obese patients, independent of pholcodine consumption, may be at an increased risk of anaphylaxis[3].

Patient uncertainty about pholcodine consumption

Patients may be uncertain about their pholcodine consumption. Prior to the recall of pholcodine-containing products, many cough suppressants were on the market. Patients are often unable to recall the specific product they consumed.

Statistical analysis of the ALPHO[3] and Sadlier[4] papers demonstrated that the positive predictive value (PPV) of questioning individual patients about their recent pholcodine consumption, and anaphylaxis to NMBAs, lies between 0.01% and 0.43%. The negative predictive value (NPV) of questioning individual patients about their recent pholcodine consumption, and anaphylaxis to NMBAs, is greater than 99.9%.

The NPV should not be used as reassurance that anaphylaxis is unlikely in the absence of pholcodine consumption. A high index of suspicion by anaesthetists is essential for early recognition and prompt treatment of anaphylaxis.

ANZCA assumes the TGA's advice to ask patients about their pholcodine use in the previous 12-months is a result of the ALPHO[3] and Sadlier[4] studies, which examined a population of patients who had consumed pholcodine in the 12-months prior to their episode of anaphylaxis. These studies did not explore how anaphylaxis rates changed within or beyond the 12-month period.

No evidence exists to identify how the risk of an individual developing anaphylaxis to a NMBA because of pholcodine consumption will change over time. Evidence from Norway suggests that following the withdrawal of pholcodine, the risk of anaphylaxis to NMBAs amongst the population continues to fall over many years and is likely never to return to the risk level of the non-exposed population[5].

Advice to anaesthetists

The above factors suggest that, while questions about a patient's recent pholcodine consumption may inform some patient-level decision-making (by prompting further discussion about anaphylaxis), routine questioning about recent consumption is unlikely to be useful for clinical decision-making by anaesthetists.

If a patient advises they have consumed pholcodine, and is concerned they may develop anaphylaxis as a result, the following information may be helpful to provide:

- The risk of anaphylaxis to NMBAs is low with likely incidences between 1:500 – 1:10 000.
- No evidence exists to show that delaying surgery for weeks or months will reduce the risk of anaphylaxis to NMBAs.
- The reason the TGA has withdrawn pholcodine from the market is to prevent future exposure to pholcodine.
- Should an episode of anaphylaxis occur, anaesthetists have the expertise to manage it due to their knowledge, skills and ongoing training.

Anaesthetists are reminded to keep up to date with current anaphylaxis management guidelines, complete the applicable Emergency Response Modules and be prepared to manage such a crisis.

References

1 https://www.tga.gov.au/news/safety-alerts/pholcodine

2 https://www.tga.gov.au/news/safety-updates/check-pholcodine-use-general-anaesthesia

3 Mertes PM, Petitpain N, Tacquard C et al. Pholcodine consumption increases the risk of perioperative anaphylaxis to neuromuscular blocking agents: the ALPHO case-control study. BJA 2023;131:150–158. https://pubmed.ncbi.nlm.nih.gov/36967281/.

4 Sadleir PH, Clarke RC, Goddard CE et al. Relationship of perioperative anaphylaxis to neuromuscular blocking agents, obesity, and pholcodine consumption: a case-control study. BJA 2021;126:940–948.

5 de Peter GH, Florvaag S, Johansson SGO et al. Six years without pholcodine. Norwegians are significantly less sensitised and more tolerant to neuromuscular blocking agents. Allergy 2017;72:813–819.