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Pholcodine, perioperative anaphylaxis, and the European Medicines Agency: finally the decision to remove pholcodine from the market in the European Union

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This editorial accompanies: Pholcodine exposure increases the risk of perioperative anaphylaxis to neuromuscular blocking agents: the ALPHO case-control study by Mertes et al., *Br J Anaesth* 2023;131:150–158, doi:[10.1016/j.bja.2023.02.026](https://doi.org/10.1016/j.bja.2023.02.026)

Summary

Two recent case–control studies, both published in the *British Journal of Anaesthesia*, have shown that intake of pholcodine-containing cough medicines during the year preceding general anaesthesia significantly increased the risk of anaphylaxis caused by neuromuscular blocking agents. Both a French multicentre study and a single-centre study from Western Australia offer strong support to the pholcodine hypothesis for IgE-sensitisation to neuromuscular blocking agents. The European Medicines Agency, criticised for not taking preventive action at its first assessment of pholcodine in 2011, finally recommended a stop to sales of all pholcodine-containing medicines throughout the EU on December 1, 2022. Time will tell whether this reduces the incidence of perioperative anaphylaxis in the EU, as in Scandinavia.

Keywords: European Medicines Agency; IgE sensitisation; neuromuscular blocking agents; perioperative anaphylaxis; pholcodine

The large multicentre Allergy to Neuromuscular Blocking Agents and Pholcodine Exposure (ALPHO) study from France by Mertes and colleagues,¹ published in this issue of the *British Journal of Anaesthesia*, shows that intake of pholcodine-containing medicines during 12 months before general anaesthesia significantly increases the risk of perioperative anaphylaxis to neuromuscular blocking agents (NMBAs).¹ A similar conclusion had recently been reported based on a single-centre case–control study from Western Australia by Sadleir and colleagues.² The findings considerably strengthen the pholcodine hypothesis of IgE-sensitisation to NMBAs, and a decisive point seems to have arrived for the pholcodine story.³

The story began in the 1950s when French chemists modified the morphine molecular structure by adding a morpholino side chain, creating a new molecule in the opioid family, known as pholcodine (3-(2-morpholinoethyl) morphine). The modification removed most of the classical pharmacological effects of morphine, including euphoria and risk of addiction, whilst a weak antitussive effect was retained. From the 1950s to date, pholcodine was included in many cough medicines, sold mostly over the counter, for non-productive cough occurring with common colds and flu. This indication allowed access to large markets with high and never-ending demands. In September 2022, according to the European Medicines Agency (EMA), 16 different

pharmaceutical companies (marketing authorisation holders) marketed a total of 34 different pholcodine-containing products in the EU alone.⁴

However, the modification rendered the new opioid pholcodine with a new and troublesome property, unforeseen at the time. Intake by tablet or liquid formulations could elicit polyclonal Immuglobulin E (IgE) responses, of which one cross-reacted with the allergenic epitope on NMBAs, the quaternary ammonium ion (QAI).⁵ Norwegian data suggested that 40% of the population had been exposed to pholcodine, of which 20–25% became sensitised, representing 10% of the entire population. Re-exposing sensitised individuals led to enormous increases in serum IgE levels by up to 100-fold.^{6,7} As a haptenic molecule, pholcodine does not activate IgE-mediated allergic responses towards itself; therefore, high IgE antibody levels go clinically unnoticed if not specifically analysed. Apart from anaphylaxis, they can confound allergy testing and prevent patients with severe allergen-driven asthma from receiving additional treatment with anti-IgE antibodies according to the 2022 Global Initiative for Asthma (GINA) update.⁸ Other untoward effects of elevated IgE levels might also exist but have not been extensively investigated. In summary, pholcodine became one of the most potent IgE-sensitising agents known.

The dominating mode of sensitising populations to pholcodine and the NMBA-reacting epitope QAI is through consumption of pholcodine-containing cough medicines. Other sensitising environmental factors might also exist, but to date,

no other candidate has been identified. Bulk national purchases of pholcodine (principally an opioid), as monitored by the United Nations International Narcotics Control Board (INCB), distinguish between countries with high or low reporting of perioperative anaphylaxis, simply by looking at national pholcodine sales per inhabitant (www.incb.org). Serological multicentre follow-up studies found statistically significant associations between national sales and IgE sensitisation to pholcodine.^{9,10}

There was also another side of the story; with the dissemination of pholcodine use came increased reporting of perioperative anaphylaxis to NMBA. The first hypersensitivity reaction to suxamethonium was reported by Smith¹¹ in 1957, followed by others in 1959.¹² In 1967, the first well-defined case of anaphylaxis to suxamethonium was published from Australia.¹³ Since then, a considerable body of epidemiological data from national anaesthesia–allergy networks on perioperative anaphylaxis has confirmed large national and regional differences in prevalence, and also identifying new causes. However, in most reporting countries where pholcodine was on the market, IgE-mediated reactions to NMBA remain a major mode of action.¹⁴

Although rare, perioperative anaphylaxis is notoriously unpredictable and challenges the skills of anaesthetic and surgical teams in operating theatres around the world. For the affected patients, apart from aborted procedures, even in these well-monitored settings, anaphylaxis represents real threats to patient health and safety. Mortality rates up to 4.1% are reported, and a third of patients surviving anaphylaxis suffer physical, psychological, and cognitive sequelae.^{15,16}

National medicines authorities have reacted differently to the mounting body of data in support of the pholcodine hypothesis. In Norway, pholcodine-containing cough mixtures were taken off the market in 2007 by choice of the single marketing authorisation holder.¹⁷ The French National Agency for Medicines and Health Products Safety (ANSM) took steps to reduce pholcodine exposure by changing the prescription status of pholcodine-containing medicines from over-the-counter to prescription only in 2011. The ANSM further proposed that the EMA's Committee for Medicinal Products for Human Use (CHMP) carry out a full assessment of the benefit–risk balance of pholcodine and issue an opinion on whether marketing authorisations should be maintained or changed across the EU.

In December 2011, after assessing the available epidemiological, serological, and interventional study data, the CHMP announced that, 'The existing evidence did not support the conclusion that the use of pholcodine-containing medicines presented a risk of developing anaphylactic reactions to NMBA, although not without divergence of opinion. It was further concluded, and successively endorsed by the European Commission in 2012, that, 'the benefits of pholcodine outweighed its risks in the treatment of non-productive cough. No new risks were identified, and patients taking pholcodine-containing medicines could continue to do so'. Nevertheless, a post-marketing case–control study was initiated to finally assess the relevance of the suggested association between pholcodine and perioperative anaphylaxis. The study was to be financed by the pharmaceutical companies marketing pholcodine-containing drugs in the EU.¹⁸

The conclusions of the EMA in 2011 were surprising and disappointing in opposing the rather uniform conclusions from the available scientific literature. Concerns and advice to reconsider the conclusion were voiced, but to no effect.¹⁹ The EMA, in this particular case, demanded more or less irrevocable scientific proof of an association between pholcodine

consumption and IgE-mediated anaphylaxis, rather than acting on qualified suspicions and extensive data to initiate measures to reduce exposure and prevent unnecessary harms to EU populations. Such measures are the same as for allergies in general: once identified, remove or at least reduce exposure to the offending allergen. In this case, exposure is proportional to sales of pholcodine. However, sales were left untouched, and exposure was allowed to continue unrestricted. Therefore, over the past decade, large numbers of EU citizens have become IgE sensitised unnecessarily; numerous perioperative anaphylactic reactions have occurred; many patients have died from anaphylaxis; and many more have suffered significant physical, psychological, and cognitive sequelae.

However, after the unmistakable results of the two recent case–control studies, the EMA has taken swift actions. Possibly a consequence of the 2016 revision of the EMA code of conduct with a focus 'to foster scientific excellence and impartiality in the evaluation and supervision of medicines for the benefit of the public and animal health'.²⁰ On December 1, 2022, the EMA Pharmacovigilance Risk Assessment Committee (PRAC), recommended revocation of the EU marketing authorisations for pholcodine-containing medicines.²¹ The decision was endorsed on December 14, 2022 by the Coordination Group for Mutual Recognition and Decentralised Procedures (CMDh) to be sent to the European Commission for a legally binding decision applicable for all EU member states. Hopefully, other agencies will follow suit, like the Australian Therapeutic Goods Administration (TGA).

The next chapter of the pholcodine story is yet to be written. According to the Scandinavian experience, EU populations at large should expect a decline in IgE-sensitisation and increasing tolerance to neuromuscular blocking agents during general anaesthesia, all within a few years.^{17,22,23} But, who will there be to write this chapter?

Declaration of interest

The authors declare that they have no conflicts of interest.

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Suspected perioperative anaphylaxis: are we making the correct diagnosis?

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Summary

We provide a commentary on aspects of a prospective study of the epidemiology of perioperative anaphylaxis in Japan (Japanese Epidemiologic Study for Perioperative Anaphylaxis [JESPA]). Accurate diagnosis of perioperative anaphylaxis is important for research but essential for clinical safety. We evaluate the diagnostic approach used in the JESPA study and