Pholcodine consumption increases the risk of perioperative anaphylaxis to neuromuscular blocking agents

Overview

Pholcodine is an opioid medicine that works by suppressing the cough reflex in the brain thus reducing the nerve signals that are sent to the muscles involved in coughing. It is used in adults and children to treat non-productive (dry) coughs and is most commonly used in cough syrups and often in combination with other active substances in products that treat the symptoms of cold and flu. Pholcodine containing products registered in Botswana are;

1. Pholtex Forte 15mg/5ml (Pholcodine)
2. Pholtex junior linctus 5mg/5ml (Pholcodine)
3. Tixylix (Promethazine & pholcodine).

Neuromuscular Blocking Agents (NMBAs) are chemical agents that paralyze skeletal muscles by blocking the movement of neurotransmitter at the neuromuscular junction (general anesthesia). NMBA medicines that are currently registered in Botswana Market for use include;

1. Troycurium 10 mg/ml injection (atracurium besylate),
2. Tracrium 2.5 mg injection (atracurium besylate),
3. Nimbex 2mg/ml injection (cisatracurium besylate),
4. Suxamethonium chloride fresenius 100mg/ml injection (suxamethonium chloride),
5. Pancon injection (pancuronium bromide),
6. Pancuronium Bromide 4mg/2ml (pancuronium bromide),
7. Curon 50mg/5ml injection (rocuronium bromide),
8. Atracurium2.5 mg injection (tracrium beyslate),
9. Atracurium 50 mg/5mg 2.5 mg injection (tracrium beyslate).

NMBAs are associated with perioperative anaphylaxis (POA). NMBA-related POA are largely unpredictable, potentially catastrophic and remain a concern for anesthesia providers. Exposure to Pholcodine causes production of antibodies (IgE) linked with fatalities during surgery. Specific IgE interacts with an epitope present in the structure of the NMBAs resulting in massive activation of mast cells and basophils hence POA. The epitope has a quaternary ammonium (QA) group, essential for the relaxant properties of any NMBAs. QAs are the main part of the allergenic structures recognized by IgE antibodies detected in most patients who experience NMBA-related POA.

Background of the safety concern

In 2011, European Medicines Agency (EMA) launched a referral procedure for the re-evaluation of the benefit/risk ratio of pholcodine. A multicenter study (ALPHO) which was a case-control study, comparing pholcodine exposure within a year before an anesthesia between patients with NMBA-related POA (cases) and control patients with uneventful an aesthesia was initiated. The ALPHO has confirmed a significant association between pholcodine consumption in the year preceding NMBA exposure and NMBA-related POA (OR adjusted=4.2 CI 95% [2.5; 6.9]).

Another monocentric case-control study conducted in Western Australia by Sadleir et al. (2021) also identified that both obesity and pholcodine consumption remained as important risk factors for NMBA anaphylaxis after correction of confounding, with pholcodine consumption associated with a very significant risk of anaphylaxis to NMBAs (adjusted OR = 12.7, 95% CI [3.8–43.1], p <.001). Other environmental factors, including occupational exposure to quaternary ammonium, should be considered in the risk of NMBA-related anaphylaxis, but they currently remain poorly defined (Sadleir et. al 2021).

Subsequent to these findings a number of National Regulatory Authorities have removed Pholcodine from their markets and these include the United Kingdom, Australia, Malaysia and South Africa and the European Union markets.

Regulatory Updates

BoMRA has assessed the available data and considered other factors to determine if the benefit-risk balance of pholcodine remain favorable. BoMRA has since concluded that the available evidence shows that the risk of using Pholcodine containing medicines outweighs the therapeutic benefits. Further, BoMRA has instructed all Marketing Authorization holders to recall all Pholcodine containing medicines out of Botswana market.

Advise to Healthcare Practitioners

- Current evidence from ALPHO study have demonstrated a clear association between Pholcodine consumption and increased risk of POA to NMBAs. Therefore, for patients scheduled to undergo general anesthesia with NMBAs, healthcare practitioners should check whether patients have used pholcodine-containing medicines in the last 12 months and maintain awareness about potential peri-anesthetic anaphylactic reaction related to NMBAs.
- Healthcare professionals are advised to re-evaluate their patients, consider other treatment alternatives.
- Inform patients that these products will no longer be available for use as a precautionary measure due to safety concerns and consider recommending appropriate alternative treatments to manage non-productive coughs.
- Report all suspected adverse events associated with NMBA- or pholcodine-containing products to BoMRA.

For more information about any medicine/vaccine safety contact, BoMRA **National Medicines Information Centre** at **373 1788/71** or email nmic@bomra.co.bw

Reference

Sadleir PHM, Clarke RC, Goddard CE, Day C, Weightman W, Middleditch A, Platt PR. Relationship of perioperative anaphylaxis to neuromuscular blocking agents, obesity, and pholcodine consumption: a case-control study. Br J Anaesth. 2021 May;126(5):940-948.