NSW Medicines Formulary Information 01/22

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Why is pholcodine not listed on the NSW Medicines Formulary?

Summary for not listing

Pholcodine is a centrally acting cough suppressant that is structurally related to morphine.[1] Efficacy data for pholcodine is lacking and pholcodine has been linked with anaesthesia anaphylaxis. These concerns have resulted in the decision to not list pholcodine on the NSW Medicines Formulary. This decision may be reviewed if supporting evidence becomes available.

Background

Pholcodine, an antitussive indicated for the symptomatic relief of non-productive cough,[2] is among the most commonly used over-the-counter (OTC) cough medicines on the Australian market. It is a codeine derivative whose mechanism of action involves depressing the medullary cough centre.

What makes pholcodine a more attractive alternative to codeine is that it has fewer adverse effects: it lacks analgesic activity and has a low potential for addiction and dependency. Unlike codeine, pholcodine is not metabolised to morphine.

Efficacy

The effectiveness of pholcodine isn't well established. A Cochrane review including 26 trials in adults and children (of variable study characteristics and quality) found that there was no good evidence for or against the use of pholcodine in the outpatient setting for an acute dry cough.[3,4]

The lack of scientific data supporting the efficacy of pholcodine has been acknowledged by both the Therapeutic Goods Administration (TGA) and European Medicines Agency (EMA) in previous reviews.[5]

Safety concerns

Pholcodine use has been shown to be a risk factor for neuromuscular blocking agent (NMBA) anaphylaxis.[6] Anaphylaxis during anaesthesia is a relatively rare occurrence, but when it occurs, it is potentially fatal.[1] In Australia, anaphylaxis during surgery has been estimated to occur in approximately 1 in 11 000 cases.[5] NMBAs are the most commonly implicated drugs in immunoglobulin (IgE)-mediated anaphylaxis during anaesthesia that can lead to perioperative morbidity and mortality. It is estimated that approximately 60% of intraoperative anaphylaxis cases are linked to NMBAs.[5]

The allergenic portion of the NMBA molecule (epitope) is thought to be the tertiary or quaternary ammonium ion (QAI). It allows specific binding of IgE to the drug, which may result in IgE-mediated anaphylaxis.

Anaphylaxis to NMBAs in Norway was observed to be approximately 10 times higher than in Sweden.[5] A closer investigation into the reasons for this found that pholcodine was not available in Sweden but was widely used in Norway. It was postulated that the substituted ammonium ion structure of pholcodine results in the increased anaphylaxis rates to NMBAs observed in Norway.[7]

As a result of this study, pholcodine was voluntarily withdrawn in Norway, leading to a reduction in NMBA anaphylaxis cases observed over the subsequent three years.[7] In concert with this, studies showed that IgE antibody titres fell to low levels within two years.[5]

Formulary review

The Australian and New Zealand College of Anaesthetists (ANZCA) together with the Australian and New Zealand Anaesthetic Allergy Group (ANZAAG) have expressed concern about the easy availability of pholcodine. As a result, the decision has been made by the both the NSW Medicines Formulary Respiratory Expert Advisory Group (EAG) and the NSW Medicines Formulary Committee that pholcodine will not be listed on the NSW Medicines Formulary.

Recommendation

Acute dry cough usually resolves without treatment. Though there is limited evidence for other available antitussives in Australia there is some evidence for honey being beneficial in adults with cough, although more studies are needed.[8] In those patients with a chronic unexplained cough (lasting more than 8 weeks), referring to a multidisciplinary cough clinic, or respiratory specialist if a clinic is unavailable, for assessment is recommended to exclude other conditions.[8]

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