Pholcodine: treatment options for dry cough

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Abstract

Pholcodine (3-O-morpholinoethylmorphine) is a centrally acting antitussive derived from morphine, used for the symptomatic relief of colds and flu in children and adults. Pholcodine is a good choice of drug to treat persistent coughs because it has a long half-life, meaning less dosage requirements, and its safety in children has been established as it is registered for use in children from age two. Although pholcodine is derived from morphine, it causes little (or no) analgesia or euphoria. After oral absorption, it crosses the blood–brain barrier to act in the medulla oblongata by inhibiting the peripheric reflexogenic receptors, also known as the "cough centre", thus increasing the threshold for coughing. Pholcodine interacts with central nervous system (CNS) depressants, monoamine oxidase inhibitors (MAOIs), neuromuscular blocking agents (NMBAs) and drugs that inhibit hepatic enzymes. Suppressants as a class are known to cause gastrointestinal and central effects; however, studies highlight that these rarely occur. Pholcodine is superior to other antitussives such as codeine because of its longer half-life, safer toxicity profile and minimal risk of addiction. The benefits of pholcodine continue to outweigh its risks, and patients can continue taking pholcodine containing medicines.

Keywords: antitussive, cough, non-productive cough, opioid pholcodine, pholtex

Introduction

Pholcodine (3-O-morpholinoethylmorphine) is an antitussive derived from morphine, used for the symptomatic relief of cough and colds in children and adults.[1,2] In South Africa (SA), pholcodine is a Schedule 6 substance; however, it becomes a Schedule 2 substance when combined with one or more active pharmaceutical ingredients in a liquid preparation and/or consisting of 20 mg pholcodine per dosage unit or less (20 mg/5 ml).[2] Currently, in SA, pholcodine is available as an over-the-counter (OTC) syrup, namely; Pholtex® Forte (15 mg/5 ml) and Pholtex® Junior (5 mg/5 ml). Other pholcodine containing OTC syrups that are combined with one or more active pharmaceutical ingredients include Pholtex® Plus containing pholcodine 5 mg, phenylephrine hydrochloride (HCl) 3.3 mg/5 ml; Docsed® containing mepyramine maleate 20 mg, codeine phosphate 5 mg, pholcodine 5 mg, ephedrine HCl 8 mg/ 5 ml; as well as Tyxylix® containing promethazine HCl 1.5 mg and pholcodine 1.5 mg/ 5 ml.[1] Given all the available cough preparations with different pharmaceutical ingredients, this article will only focus on pholcodine.

Indication

Pholcodine, an antitussive/cough suppressant, is used to treat dry and non-productive persistent coughs.[3,4] Coughing provides the benefit of removing pollen, dust, viscous fluids, and inflammatory cells from the upper airways.[5] However, a non-productive persistent cough could cause unfavourable effects such as loss of sleep, pneumothorax, rupture of surgical wounds, syncope or even rib fractures.[5] Table I gives an overview of the rational use of pholcodine.

An acute cough is a daily cough that lasts for fewer than three weeks, and when this is a dry cough, without any mucous production, pholcodine may be a suitable treatment option.[6] It is not recommended to use pholcodine on a chronic basis.

Mechanism of action

When the sensory receptors of the glossopharyngeal and vagus nerves that innervate the mucous membranes of the lower larynx, pharynx, trachea, and smaller airways of the respiratory tract are stimulated, usually, the resulting effect would be a cough.[7] Upon stimulation, a signal is transmitted from the receptor to the cough centre in the brain, which stimulates a reflex motor response that leads to the contraction of expiratory muscles, causing a person to cough.[7] Centrally acting opioid-like cough suppressants, e.g. codeine, or pholcodine, work on the coughing centre in the central

Table I: Indication for pholcodine[4-6]

Non-productive dry cough	Pholcodine indicated	Pholcodine is not indicated for productive wet cough
Postnasal drip	Short-term; treat the underlying condition	Chronic bronchitis
Viral infection (common cold)	Short-term with other symptomatic treatment	Air pollutants/irritants
Gastro-oesophageal reflux disease (GORD)	Not indicated; treat GORD	Asthma and allergic conditions
Medication-induced coughing (ACE-I)	Not indicated long term; change ACE-I to ARB	Aspiration
Heart failure	Not indicated	Lung cancer
Psychological causes	Short term until the underlying condition is treated	Pneumonia and TB

nervous system (CNS) and reduce the discharge of nerve impulses to the muscles that facilitate coughing. Codeine is no more effective than other centrally acting opioids in suppressing cough and is associated with a higher incidence of adverse effects.[8]

Although pholcodine is a centrally acting opioid antitussive derived from morphine, it causes little (or no) analgesia or euphoria.[2] After oral absorption, it crosses the blood–brain barrier to act in the medulla oblongata by inhibiting the peripheric reflexogenic receptors, also known as the "cough centre", thus increasing the threshold for coughing.[7] The effect of pholcodine is selective on the cough centre and does not affect the respiratory centre.[9]

Pharmacokinetic parameters

Pholcodine is metabolised extensively in the liver with little or no conversion to morphine, unlike codeine.[2] It is longer acting than most antitussives.[2] It is as effective as codeine; however, pholcodine has a longer elimination half-life of 32–43 hours, thus reducing dosage requirements.[2] It is removed from the body at a much slower rate than other opioids, and saliva concentrations become 3–4 times higher than plasma concentrations.[10] Pholcodine has a morpholino side chain; this structural modification provides the benefit of not causing any respiratory depression, euphoria, CNS excitation and addiction.[10]

Cautions and contraindications

Opioids interact with endogenous opioid receptors in the body, including mu, delta and kappa receptors found in the respiratory centre.[11] They decrease the stimulation of the respiratory centre by reducing carbon dioxide levels (hypercapnic drive) without producing an effect on the hypoxic drive.[5] Opioids also decrease the respiratory rate and tidal volume, thus causing the rate of breathing to decrease to three or four breaths per minute during an opioid overdose.[5] Therefore, like other opioids, pholcodine should not be used in patients with respiratory depression, asthma, chronic obstructive pulmonary disease (COPD), bronchiolitis, bronchiectasis, emphysema, and respiratory failure.[2] Pholcodine is cleared from the body at a slower rate and should not be used in patients with a liver impairment since the clearance would be slower, leading to an increased risk of unpleasant side effects.[2,10,11] It is also contraindicated in pregnancy (especially preparations containing alcohol), lactation, intolerance, or hypersensitivity to pholcodine.[12] It is safe for use in children two years and older but should be used with caution.[2,3]

Drug interactions

When taken concomitantly with alcohol, phenothiazines, benzodiazepines and tricyclic antidepressants at higher doses, pholcodine may aggravate the CNS depression of these drugs.[2] As mentioned before, pholcodine is extensively metabolised in the liver; therefore, drugs that inhibit the cytochrome P450 enzymes will lead to the increment of its levels.[2] All antitussives, such as codeine, dextromethorphan and pholcodine, are not recommended with monoamine oxidase inhibitors (MAOIs). Severe reactions, including excitations, hyperpyrexia, hypertension and death, have resulted from the concomitant use; therefore, pholcodine should not be administered while on MAOI therapy or within 14 days of discontinuation.[2] There was concern that pholcodine-containing cough syrups increase immunoglobulin E antibodies against neuromuscular blocking agents (NMBAs). However, after a lengthy review process, the European Medicines Agency (EMA) concluded that the evidence of a link between pholcodine and NMBA-related anaphylaxis is circumstantial and not entirely consistent. The EMA further concluded that, based on currently available information, the benefits of pholcodine in the treatment of non-productive cough outweigh the risks.

The EMA's Committee for Medicinal Products for Human Use concluded on the safety and efficacy of pholcodine:[10]

- the benefits of pholcodine continue to outweigh its risks;
- there have not been any new risks discovered with pholcodine;
- there is credible information on cross-sensitisation between pholcodine and NMBAs; however, the data available are weak; and
- patients can continue taking pholcodine containing medicines.

Side effects

Although rare, side effects of pholcodine and other antitussives include dizziness and gastrointestinal effects, but with overdose, respiratory depression, confusion and excitation can occur.[2] Other side effects include drowsiness, restlessness, nausea and vomiting, ataxia and skin rash.[1]

Addiction to cough suppressant syrups

In some opioid-containing antitussives, like codeine and dextromethorphan, abuse of and addiction to the preparations have been documented.[2] There is an increasing incidence of the abuse of OTC medication, for example, opioid-containing cough preparations, both nationally and internationally, which may warrant their up-scheduling.[13,14] However, pholcodine is superior to other antitussives such as codeine because of its longer duration of effect, safer toxicity profile and minimal risk of addiction.[15]

The toxic dose following pholcodine's misuse is 4 mg per kg body mass in both adults and children, during which symptoms such as agitation/anxiety, confusion/aggression, euphoria, hallucinations, nightmares/excessive dreaming, bradycardia, hypo-

tension, bronchospasms/wheezing, slow/depressed respiration, constipation, nausea/vomiting, convulsions, depressed level of consciousness/coma, involuntary movements/tremor, hypothermia, enlarged/small pupils, widespread redness or flushing of the skin, can be experienced.[16] The drugs of choice in managing opioid dependence include naloxone, buprenorphine, methadone and naltrexone.[7]

Dosing/Administration

In SA, the adult dose of oral pholcodine is 5–10 mg 3–4 times daily.[2] Lower doses such as 5 mg three times daily are recommended in patients with liver disease and the elderly.[2] In patients with renal impairment, dose reduction or increased dosing intervals are needed because of pholcodine's long elimination half-life.[2] The dose of oral pholcodine in paediatrics, from 1–5 years, is 2.5 mg three times daily, then older than five years, it is 2.5–5 mg 3–4 times daily.[2,6,7]

Conclusion

Although pholcodine is derived from morphine, it has not been documented to cause analgesia, euphoria or addiction. This makes it a suitable effective antitussive for the symptomatic relief of non-productive coughs. In addition, it rarely causes side effects; however, due to it still being an opioid, it is essential to monitor for signs of an overdose such as respiratory depression, confusion, excitation, and sedation.

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