Medicines Adverse Reactions Committee

Meeting date	5/12/2019	Agenda item	3.2.1
Title	**Pholcodine: benefit-risk review**		
Submitted by	Medsafe Pharmacovigilance Team	Paper type	For advice
Active ingredient	**Product name**		**Sponsor**
Pholcodine	Benadryl Dry, Tickly Cough, Oral solution 1mg/mL		Johnson & Johnson
	Duro-Tuss Dry Cough Liquid Forte, Oral solution 3 mg/ mL		iNova Pharmaceuticals
	Duro-Tuss Dry Cough Liquid Junior, Oral solution 1 mg/mL New Formula		iNova Pharmaceuticals
	Duro-Tuss Dry Cough Liquid Regular, Oral solution 1 mg/mL New Formula		iNova Pharmaceuticals
	Pholcodine Linctus BP, Linctus 5 mg/5mL (AFT)		AFT Pharmaceuticals Ltd
	Pholcodine Linctus BP, Linctus 5 mg/5mL (PSM)		PSM Healthcare Ltd trading as API Consumer Brands
	Pholcodine Strong BP, Linctus 10 mg/5mL (PSM)		PSM Healthcare Ltd trading as API Consumer Brands
	Strong Pholcodine Linctus BP, Linctus 10 mg/5mL Pinewood		AFT Pharmaceuticals Ltd
	Stubborn Dry Tickly Cough (Pharmacy Health), Linctus 2 mg/mL		PSM Healthcare Ltd trading as API Consumer Brands
Phenylephrine; Pholcodine	Duro-Tuss Phenylephrine PE Dry Cough + Nasal Decongestant, Oral solution		iNova Pharmaceuticals
Cetylpyridinium; Pholcodine	Duro-Tuss Dry Cough, Lozenge (Lemon)		iNova Pharmaceuticals
	Duro-Tuss Dry Cough, Lozenge (Orange)		iNova Pharmaceuticals
Bromhexine; Pholcodine	Duro-Tuss Cough Liquid Expectorant, Oral solution 0.8mg/1mg per mL		iNova Pharmaceuticals
Benzydamine; Cetylpyridinium; Pholcodine	Difflam Anti-Inflammatory Lozenges with Cough Suppressant, Lozenge Blackcurrant Sugarfree		iNova Pharmaceuticals
PHARMAC funding	Pholcodine liquid 1 mg per ml (any brand) – Hospital Medicines List		
Previous MARC meetings	Meeting 132 (Dec 2007) Safety and efficacy of cough and cold medicines for use in children Meeting 138 (Jun 2009) Safety and efficacy of cough and cold medicines for use in children		

	Meeting 143 (Sep 2010) Consideration of antitussive-expectorant and antitussive-mucolytic combination cough and cold medicines under Section 36 of the Medicines Act 1981
International action	EMA review benefit-risk balance of pholcodine in 2011 and recommended maintenance of the marketing authorisation, but concluded that further investigation of an association between pholcodine use and NMBA-associated anaphylaxis is needed, and required MAHs to conduct a case-control study. https://www.ema.europa.eu/en/documents/referral/pholcodine-article-31-referral-assessment-report_en.pdf
Prescriber Update	Medicines Classification Update: November 2018 (Prescriber Update 40 (2): 35-36)
Classification	Pharmacy-only medicine
Advice sought	**The Committee is asked to advise:** • on the evidence of efficacy • on the evidence for safety • the strength of the evidence that pholcodine predisposes patients to anaphylaxis with NMDAs (all or a subset) • whether the balance of benefits and risk for the use of pholcodine for the symptomatic treatment of non-productive cough is favourable • any regulatory action is required to improve the balance of benefits and risks

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1 PURPOSE

The purpose of this paper is to review the balance of benefits and risks of harm of pholcodine. In particular, the paper will examine the evidence for an association between pholcodine and an increased risk of anaphylaxis with neuromuscular blocking agents (NMBAs). The Medicines Classification Committee (MCC) reviewed the classification for pholcodine at their 61st meeting in November 2018. Although the Committee did not recommend any change to the classification of pholcodine, they requested Medsafe to perform a review of the benefits and risks of harm (https://www.medsafe.govt.nz/profs/class/Minutes/2016-2020/mccMin2Nov2018.htm).

2 BACKGROUND

2.1 Pholcodine

2.1.1 Substance

Pholcodine is an alkyl ether of morphine in which the phenolic hydrogen atom is replaced with a morpholinoethyl group [1]. There is a high degree of structural similarity between pholcodine and both morphine and codeine, as illustrated in Figure 1 and Figure 2. All three molecules contain the same fused pentacyclic structure, but the free hydroxyl group in the morphine molecule is substituted by a methyl group in codeine, and by a morpholinoethyl group in pholcodine.

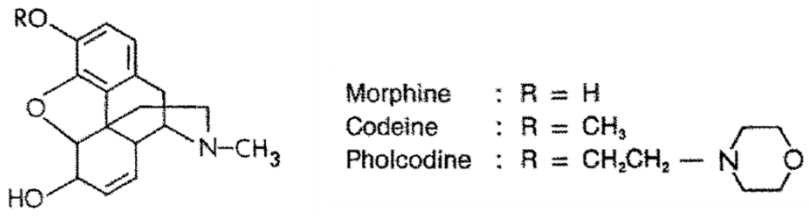


Figure 1. Chemical structures of morphine, codeine and pholcodine [1]

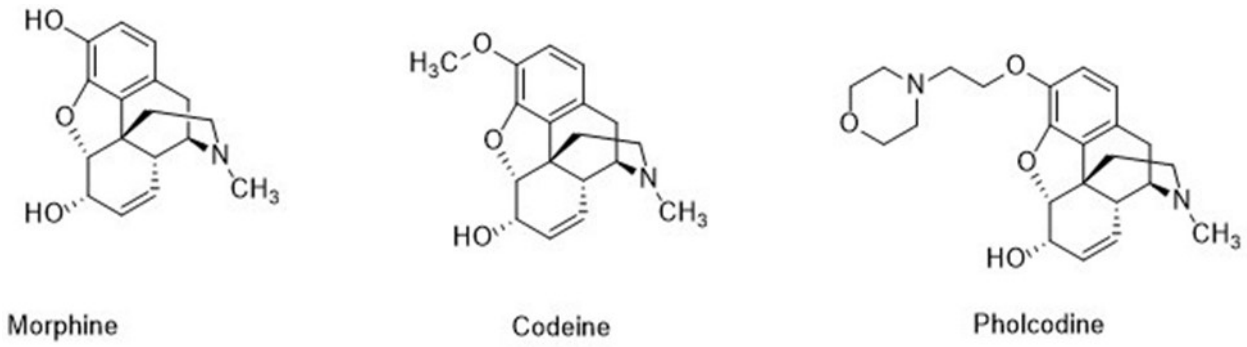


Figure 2. Comparison of molecular structure between pholcodine, morphine and codeine (compiled from https://www.drugbank.ca)

The bulkier morpholinoethyl group on the pholcodine molecule may account for observed differences in pharmacokinetics between pholcodine and either codeine or morphine [2].

Pholcodine is a 'grand-fathered' medicine, as it was in use at the time that the Food and drug Act 1969 and subsequent Medicines Act 1981 came into force. Consequently, clinical safety and efficacy data have not been reviewed by Medsafe for pholcodine-containing products. Pholcodine is classified as a Pharmacy-Only medicine.

Pholcodine is available in several different formulations, either as a single active ingredient or in combination with other cough and cold medicines, as outlined above.

2.1.2 Pharmacokinetics

As pholcodine is a Pharmacy-Only medicine, data sheets are not mandated and none have been provided to Medsafe.

The UK SmPC for pholcodine Linctus [3] states:

> *Maximum plasma concentrations are attained at 4 to 8 hours after an oral dose. The elimination half-life ranges from 32 to 43 hours and volume of distribution is 36-49L/kg.*
>
> *Pholcodine is protein bound to the extent of 23.5%.*
>
> *Pholcodine is metabolised in the liver but undergoes little conjugation.*

Pharmacokinetic (PK) data for pholcodine mainly comes from two studies carried out in the 1980s.

Chen *et al* [4] studied the PK of pholcodine after single oral doses of 20 mg and 60 mg three weeks apart, and repeated doses of 20 mg 8 hourly for 10 days in six healthy volunteers. The results of this study are summarised in Table 1.

An earlier study by Findlay *et al* [2] in six healthy male volunteers following a single 60 mg dose of pholcodine suggested a longer t_{max} (5.8 ± 0.8 h) and lower AUC (1.00 ± 0.08 mg*h/L), although the mean plasma elimination half-life was similar (37 ± 4 h). Table 1

Table 1. Pharmacokinetics of pholcodine

Dose	t_{max}	C_{max}	AUC (mg*h/L)	$t_{1/2}$ (h)	Excretion of dose (%)
Chen 1988					
20 mg single dose	2.0 ± 1.3	12.8 ± 6.3	0.72 ± 0.16	45.4 ± 6.8	27 ± 3
60 mg single dose	1.3 ± 0.9	26.3 ± 6.4	1.67 ± 0.31	51.9 ± 11.8	24 ± 3
20 mg q8h for 10 d			0.55 ± 0.06		26.8 ± 3.5
Findlay 1986					
60 mg single dose	5.8 ± 0.8	57.1 ± 11.0	1.00 ± 0.08	37 ± 4.2	

Compiled from Chen et al 1988 [4] and Findlay et al 1986 [2]

Approximately 23.5% of pholcodine is protein bound. Chen *et al* calculated the volume of distribution to be 30-40 L/kg, assuming complete bioavailability.

Pholcodine is metabolised in the liver. Maurer and Fritz [5] postulated four partly overlapping phase I metabolic pathways for pholcodine based on its urinary metabolites:

- N-demethylation,
- N-desalkylation at the morpholino ring followed by reduction of the resulting aldehyde to the desmorpholino-hydroxy metabolite,
- oxidation of the morpholino ring to the hydroxy and oxo metabolite, and
- O-desalkylation to morphine.

With the exception of the morphine metabolite, pholcodine and its phase I metabolites were not converted to enzyme-hydrolysable conjugates.

Although conversion to morphine has been postulated, morphine was not detected in the urine and plasma samples following pholcodine administration in the PK studies described above [2, 4].

Maurer and Fritz also showed that pholcodine itself is detectable in the urine 5-7 weeks after ingestion. The desmorpholino-hydroxy metabolite can be detected 1-2 weeks after ingestion but the other metabolites are only detectable in the first few hours. The lipophilic structure of pholcodine is believed to contribute to its low rate of metabolism and slow elimination.

The renal clearance of pholcodine was 137 ± 34 ml/min, and was inversely correlated with urine pH, but not with urine flow rate. Approximately 25 percent of the dose is excreted unchanged by the kidneys [4].

Comments:
The recommended adult dose of pholcodine is 5-15 mg per dose, no more than 4 doses in a 24 hour period. The reason for this frequent dose regimen is not clear. The half-life of pholcodine reported in the early PK studies ranged from 37 ± 4.2 h to 51.9 ± 11.8 h, which suggests that a longer dose interval would be appropriate.

2.1.3 Pharmacodynamics

Pholcodine is a cough suppressant with a mild sedative effect but little analgesic activity [3].

2.2 Product prescribing and labelling information

2.2.1 New Zealand

The Label Statements Database (https://www.medsafe.govt.nz/regulatory/labelling.asp) lists the warning and advisory statements that are required on medicine and related product labels under regulations 13(1)(i) and 14(1)(f) of the Medicines Regulations 1984. Pholcodine is required to carry the following statements:

- Do not use in children under 6 years old.
- Consult a healthcare professional before using in children aged six years and over.
- Do not use with other medicines intended to treat the symptoms of the common cold except on the advice of a healthcare professional.

2.2.2 Australia

Pholcodine 1mg/ml is classified as a S2 – Pharmacy Medicine in Australia. An OTC Medicine Monograph is available on the TGA's website for pholcodine (available at: https://www.tga.gov.au/otc-medicine-monograph-pholcodine). The monograph does not include information on efficacy or safety.

2.2.3 United States

Pholcodine is classified as a Schedule 1 drug in the US. This classification is used for drugs, substances or chemicals with no currently accepted medical use and a high potential for abuse. Other examples include: heroin, lysergic acid diethylamide (LSD), marijuana (cannabis), 3,4-methylenedioxymethamphetamine (MDMA, ecstasy) and mescaline (peyote).

https://www.dea.gov/drug-scheduling

https://www.deadiversion.usdoj.gov/schedules/orangebook/c_cs_alpha.pdf

2.2.4 UK

Pholcodine is classified as a Pharmacy Medicine in the UK. SmPCs and Patient Information Leaflets are available for various pholcodine-containing products in the UK at https://www.medicines.org.uk/emc.

3 SCIENTIFIC INFORMATION

3.1 Efficacy

Most of the efficacy studies for pholcodine were conducted before 2000. The published literature on pholcodine efficacy is presented below and summarised in Table 8.

3.1.1 Snell and Armitage, 1957 (Lancet)

Clinical comparison of diamorphine and pholcodine as cough suppressants by a new method of sequential analysis [6]

This trial was designed to test the effect of diamorphine (heroin) on cough by comparing it with pholcodine and placebo using a pairwise comparison called 'sequential analysis'. The study medicines included:

- Diamorphine gr. 1/20 per 60 minims *(approx. 3.2 mg in 3.5 ml)* with oxymel, glycerine and syrup
- Pholcodine 4 mg+ antazoline 12.5 mg + ipecac 0.03 *(units not clear)* + sucrose 3.20 g *(per 120 minim dose)*
- Placebo – oxymel, glycerine and syrup (identical to diamorphine linctus).

Each mixture was taken for two consecutive days in a dose of minims 120 *(approx. 7 ml)* at night before bed, with the three courses completed over 6 consecutive days. The order in which the medicine was administered was blinded to the patients, nurses and observer. The six possible medicine orders were distributed randomly among each succeeding group of six patients.

Patients were told that they were receiving three types of medicine and that they would be asked to rank them in order of preference. They were then asked to note the severity of their cough from the time of taking the medicine until going to sleep.

The authors noted that *'early in the trial it became clear that patients were rarely able to give a clear set of preferences, because they usually gave a tie for first or last place or even for all three mixtures'*. Instead, they decided to compare treatments in pairs using for any one pair of treatments only those patients who gave a clear preference in favour of one or other treatment.

Comments:

The method used in this study is fundamentally flawed, as it excluded all patients who found no difference between treatment options.

Furthermore, pholcodine was given in a preparation that contained an antihistamine and an expectorant, so even if the method had been robust, it would not be possible to draw any conclusions on the efficacy of pholcodine in this group of patients with cough of various types and aetiologies.

3.1.2 Bickerman and Itkin, 1960 (Clinical Pharmacology and Therapeutics)

Further studies on the evaluation of antitussive agents employing experimentally induced cough in human subjects [7]

This study looked at the feasibility of inducing cough using citric acid aerosols to assess the antitussive effect of medicines in healthy subjects. Thirteen coded drugs were tested on 'trained' healthy subjects. The subjects were 16 healthy technicians and research fellows (8 male and 8 female; mean age 34 years), who had been employed in previous antitussive studies during the preceding 5 years. For each participant, a 'threshold' concentration of citric acid aerosol required to induce cough had previously been established. The threshold was re-determined for each subject during the 'test run' in this study. On the test day, subjects were selected who had no evidence of throat irritation or upper respiratory infection. A baseline measure (control) was obtained after administering five inhalations of the appropriate concentration of citric acid aerosol with a rest period for 1-2 minutes between each inhalation. Immediately after the control run, the drug to be tested was administered orally and studies were performed at hourly intervals for a period for 4 hours. With the same procedure, two preparations, A' placebo and dihydrocodeinone resin, were retested over a 7 hour period.

Graphic tracings of the cough response elicited by the aerosol were obtained with a pneumotachograph and a microphone, which recorded the peak and mean flow rates of air expelled with cough and the sound pressure wave, respectively. The frequency or number of coughs per stimulus could be determined from either the microphone or pneumotachographic tracings.

The 13 drugs were coded alphabetically and administered to each subject in random sequence as identical white capsules in a double-blind manner. When decoded on completion of the study, three of the preparations were found to be placebo. One of the agents tested was morphinolinylethylmorphine (pholcodine).

Data for cough frequency and intensity were obtained in response to a total of 3745 inhalations of citric acid aerosol, including 750 for the three placebos and for pholcodine. Other drugs were also tested in this study to determine the effectiveness of the testing method.

Measurements derived from the graphic tracings of the cough responses were subjected to statistical analyses, described as follows:

> *'Measurements derived from the graphic tracings of the cough responses elicited by a total of 3,745 inhalations have been subjected to statistical analyses by use of the 3 factor analysis of variance in which the subject, hour, and order of stimulus are integrated. Statistical significance for each drug has been indicated at the 95 per cent confidence limit by conversion of the F-values into a percentile variation about the mean per cent changes from the control level for each hourly period. Thus any effect resulting from chance would occur less than one time in twenty.'*

None of the three placebos showed any significant suppression in the frequency of cough over the 4 hour period, with the exception of E' Placebo in the first hour response. In a review of the data for each of the subjects tested against *E',* it was noted that one subject had a marked reduction in the number of coughs from 18 to 6 at the first hour period. This could not be explained. When this discrepancy was corrected for, the mean change for the first hour was 17 percent.

Pholcodine 10 mg dose showed a significant reduction in cough over the 4 hour test, with a mean reduction of approximately 26% for each of the first three hours and 21% for the fourth hour. Over the entire four-hour period, the effect was approximately equivalent to that achieved with codeine 15 mg (Figure 3).

Comments:

The focus of this study was not to compare the efficacies of the various cough medicines, but to test the effectiveness of the testing method itself. Each drug was tested in a subset of the total 16-person study population. Analysis was performed on the pooled tracings from these subjects, and was not studied at the individual subject level. There was no direct analysis of pholcodine vs placebo or vs codeine in individual subjects. It is difficult to draw any conclusions on the clinical efficacy of pholcodine from this study.

3.1.3 Heffron, 1961 (Journal of New Drugs)

Preliminary Evaluation of Pholcodine, A New Antitussive Agent [8]

This was an uncontrolled, non-blinded study of pholcodine in 54 prison inmates aged 21 to 65 years with acute or chronic cough of various aetiologies (including both productive and non-productive cough)

Nineteen inmates with acute cough (2-6 weeks duration) were enrolled in the study. The cause of acute cough was reported to be acute (6) or sub-acute (3) bronchitis, other upper respiratory infection (8), chest cold (1) or undetermined (1). A further 35 inmates with chronic cough (months to years) were also enrolled in the study. The cause of cough among these participants was reported to be bronchitis (19), bronchiectasis (7), arrested tuberculosis (5), emphysema (3) and lung carcinoma (1).

Participants with acute cough were started on pholcodine at a dose of 1-2 x 5 mg tablets (depending on severity of cough) every four hours, and the dose was increased depending on response. Participants with chronic cough were started on pholcodine at a dose of 2 x 5 mg tablets and the dose was increased as the study proceeded. Pholcodine was stopped when the cough subsided.

Response to pholcodine was assessed as 'excellent', 'good', 'fair' or 'poor'. Response was assessed as 'excellent' if cough subsided completely of markedly within 48 hours for acute cough, or within two weeks for chronic cough and was sustained for the duration of the study. A 'good' response was defined for acute cough as some immediate improvement and substantial relief in a few days, and for chronic cough as sustained moderate relief. For both categories of cough, a response was assessed as 'fair' if there was slight relief from cough, and 'poor' if there was no response.

Fifteen of the 19 patients with acute cough had an 'excellent' or 'good' response following administration of pholcodine 10 mg to 60 mg daily (most received 30-60 mg daily in 3-4 divided doses) for two days to two weeks (mean duration seven days).

Twenty-seven of the 35 patients with chronic cough had an 'excellent' or 'good' response following administration of pholcodine 20 mg to 100 mg daily for up to seven months.

Side-effects were reported as minimal among the 19 patients with acute cough. Two patients complained of nausea, including one who refused medication after the second day. In the other, nausea subsided after the first day of therapy. A third patient with acute cough reported a burning sensation in the chest and throat, but was not bad enough to interfere with therapy. Side-effects were more frequent among patients with chronic cough, but mainly occurred during the first few days of therapy and none were severe enough to warrant discontinuation of pholcodine. Reported adverse effects included 'gas', nausea, diarrhoea, and anorexia. Several participants in both groups reported a slight tranquilizing effect.

Five participants with chronic cough had a history of narcotic drug addiction. Pholcodine was stopped abruptly for two week period after they had received the medicine for three to four months. Pholcodine was also stopped abruptly in a further two participants with a history of drug addiction who were in the acute cough group and had received pholcodine for a few weeks. None of these former addicts reported withdrawal symptoms when pholcodine was stopped.

Comments:

This study was not placebo or active controlled and was not blinded. The pholcodine dose administered during the study was not standardised and ranged from 10 mg to 60 mg daily for acute cough and from 20 mg to 100 mg daily for chronic cough. Patients were observed for variable periods of time ranging from a few days to 7 months.

Without a placebo control, it is not possible to know to what extent pholcodine contributed to the relief of cough, particularly in participants with acute cough due to a self-limiting respiratory tract infection.

Concurrent medicines were not reported, although it was noted that one patient with allergic bronchitis experienced excellent relief with two tablets every three hours in combination with potassium iodide expectorant.

A key focus of this study appears to have been on the addictive potential of pholcodine. Many of the study participants had a history of opiate addiction. Pholcodine was suddenly withdrawn during the study to observe whether the patients experienced symptoms of withdrawal. The value of testing the addictive potential of pholcodine in an inmate population that has been sensitised to much stronger opiates is questionable.

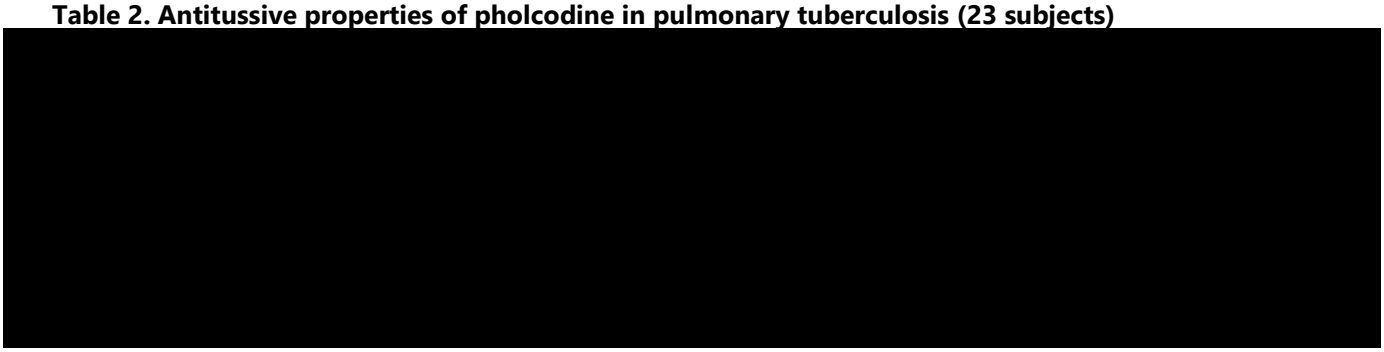
3.1.4 Mulinos, Nair *et al*, 1962 (New York State Journal of Medicine)

Clinical Investigation of Antitussive Properties of Pholcodine [9]

This study compared pholcodine with codeine and placebo in 23 hospital in-patients (7 female, 16 male) aged 25 to 71 years (mean 46 years) with chronic persistent cough associated with pulmonary tuberculosis.

Patients were administered either pholcodine or codeine 10 – 20 mg, or placebo, two to four times per day for one to 29 days. The report describes a *'comparative study on the same subjects … with a placebo or codeine sulphate, given in equivalent dosage units, frequency and form…'*, but the exact protocol is not stated. The results shown in Table 2 are described as follows: *'Although the day-to-day responses were not always uniform, the superiority of pholcodine and codeine sulphate over the placebo was immediately evident. The low incidence of favourable responses from the placebo is attributable to the chronicity of the cough and the critical attitude of the subjects towards cough medications.'*

Table 2. Antitussive properties of pholcodine in pulmonary tuberculosis (23 subjects)



A second group of 26 patients (10 female, 16 male) aged 21-65 years (mean 44 years) received the three preparations alternately within a one week period. The drugs were administered only once a day in the evening. On the morning following each administration, data on the frequency and severity of cough, the occurrence of side effects were immediately recorded on the chart. The ward physician assessed the antitussive effects of each preparation based on any expression of preference by the patients. Patients were apparently unaware which preparation they were receiving, but it is not clear whether or not the ward physician was also blinded to the study medicine.

Fourteen patients expressed preference for pholcodine over codeine, and none expressed preference for the placebo, regardless of the order of administration (Table 3). The data was also described as showing *'a positive*

dose-related graduation of antitussive response to the two active preparations and usually no response, with a return of the cough, after the administration of the placebo'.

[redacted]

Patients slept better following both pholcodine and codeine sulphate, but this was ascribed to the alleviation of the cough.

The authors concluded:

'…pholcodine administered orally to patients with a cough in tablets containing 10 mg had antitussive properties which were superior to those seen from the use of an equal dose of codeine sulphate'.

Comments:

The design and protocol of the first study is not clear. Of the 23 patients included in the study, 16 received pholcodine for an average of 9.6 (range 5-14) days, 17 received codeine for an average of 9.1 (range 1-29) days and 18 received placebo for an average of 7.6 (range 3-14) days.

The second study appears to have been a cross-over study.

Close examination of the study results draws into question the authors conclusion that pholcodine had antitussive properties that were superior to codeine. Table 3 shows that for pholcodine, 15/23 (65%) patients who received 10 mg and 21/22 (95%) who received 20 mg experienced a complete or marked response. For codeine, 20/24 (83%) patients who received 10 mg and 22/22 (100%) patients who received 20 mg experienced a complete or marked response. In contrast to the authors' conclusion, these results suggest that codeine had superior antitussive effects compared to pholcodine. Furthermore, overall 24/47 (51%) of patients receiving placebo experienced a complete or marked response.

There seems little justification for the authors' conclusion that pholcodine has superior antitussive properties compared to codeine. Furthermore, as no statistical analysis was reported, the significance of its apparent superiority over placebo is not clear.

3.1.5 Rose, 1967 (Practitioner)

Pholcodine plus pseudoephedrine in the treatment of cough. A controlled trial. [10]

A randomised, double-blind cross-over study comparing pholcodine + pseudoephedrine with codeine in 45 patients (35 male, 10 female) with *'some degree of chronic respiratory disease'* in a general practice setting in the UK. Of the 45 patients, 42 had a combination of cough and breathlessness, two had cough and one had breathlessness. No further information on the underlying cause of the cough or breathlessness was provided. Information on the age and sex distribution of the patients is not available.

The study medicines were:

- pholcodine 15 mg + pseudoephedrine 60 mg linctus ('sednine') – trial preparation
- codeine 15 mg linctus - control

Each patient received each preparation for one month at an unstated dosing frequency. Both patient and doctor were blinded to the order of administration, which was determined by a random code.

Patients were assessed for severity of cough and breathlessness at the start of the trial and after each course of treatment using a questionnaire. The physician also assessed the patient's improvement after each course of treatment.

The following scale was used to assess cough and breathlessness: 0=absent, 1=slight, 2=moderate, 3=severe, 4= very severe. The score was derived by taking the change from the starting value and reversing the sign. For example, a change from severe (3) to slight (1) would score a +2 (ie, 3→1, difference is -2, reverse sign→+2).

Overall assessment was based on the scale: -1=worse, 0=unchanged, 1=slight improvement, 2=moderate improvement, 3=marked improvement to complete relief, between the beginning and end of each treatment period.

Twenty-three patients had the trial preparation in the first treatment period and 22 patients had the control. The study results are shown in Table 4.

The author reported that the trial preparation (pholcodine-pseudoephedrine linctus) gave more relief of both cough and breathlessness and greater improvement in overall assessment than did the control preparation (codeine linctus), regardless of the order of administration. It was also noted that the trial preparation performed relatively better when given first and the control when given second. This observation was attributed to a tendency in cross-over trials for the effectiveness of one treatment is reflected in that of the next.

Comments:

It is not possible to assess the efficacy of pholcodine from this study as it was given in combination with pseudoephedrine. The study is also limited by the lack of a placebo arm.

3.1.6 Edwards, Lewis *et al*, 1977 (British Journal of Diseases of the Chest)

The effect of pholcodine with and without an antihistamine on cough and expectoration [11]

Twenty-four adult patients with cough and sputum due to chronic bronchitis were admitted serially to a single bedded hospital side-ward where they were observed for five consecutive days. The patients were routine attenders at the Leeds Chest Clinic complaining of persistent cough and sputum > 10 ml/24 h. The patients were not experiencing an acute exacerbation at the time of observation, and did not require concurrent antibiotic or other specific therapy.

Each patient was admitted at 18.00 h on the day before the investigation began. Chest x-ray and FEV_1 were performed on admission, and sputum volume was measured from 09.00 h each day. Throughout the five 24-hour observation periods starting from 09.00 h on the first morning in hospital, all coughs were recorded by tape-recorder, so that the total coughs in each half-hour could be counted. No medicines were given on the first day (control). On each subsequent day, the patients were given one of four different study medicines, prescribed for 24 hours only and allocated in random order. No other treatment was used during the five days. The study medicines included:

- Pholcodine 15mg + phenyltoloxamine 10 mg / 5 ml – a proprietary preparation (Pholtex) in which both pholcodine and the antihistamine phenyltoloxamine are attached to ion-exchange resins to give slow release and prolonged action *(referred to as 'Pholcodine compound')*
- Pholcodine 15 mg with ion-exchange resin (long-acting)
- Pholcodine 15 mg without ion-exchange resin (short-acting)
- Placebo – identical appearance, syrup base only

A 5ml dose was given at 09.00 h and 21.00 h on each test day, allotted sequentially according to a table of random entry prepared to ensure that each preparation was used an equal number of times on the 2nd, 3rd, 4th and 5th day after admission.

Cough was recorded using a cough-actuated microphone. Two sets of data were generated: the mean cumulative cough bouts over 24 hours and the total coughs in each 2-hour interval (Figure 4Figure 5).

Statistical significance was tested using Student's *t*-test and Friedman's non-parametric test (Table 5).

Pholcodine + phenyltoloxamine was more effective than pholcodine alone (either resinated or unresinated) in reducing both bouts of coughing and total number of coughs.

No significant differences were observed in the mean daily sputum volumes between the four treatments.

These findings lead the authors to conclude that the beneficial effect of the compound preparation of pholcodine with phenyltoloxamine was largely due to the antihistamine constituent. To their surprise, pholcodine produced an insignificant reduction in cough frequency.

Comments:

This apparently well-conducted and well-reported study of 24 adult patients with chronic bronchitis compared the cough and sputum reduction efficacy of pholcodine alone and in combination with an antihistamine. The study found that pholcodine alone did not reduce productive cough in this patient group.

Pholcodine is mainly marketed in New Zealand for the relief of dry cough. There are no approved products containing pholcodine in combination with an antihistamine.

Pholcodine is available as a single active ingredient preparation or in combination preparations containing phenylephrine (decongestant), or with cetylpyridinium (antiseptic) either with or without benzydamine (topical anti-inflammatory).

3.1.7 Jaffé and Grimshaw, 1983 (Current Medical Research and Opinion)

Randomized single-blind trial in general practice comparing the efficacy and palatability of two cough linctus preparations. 'Pholcolix' and 'Actifed' Compound in children with acute cough. [12]

This study is reported to be a randomised, single-blind study comparing the efficacy and palatability of 'Pholcolix' and 'Actifed' Compound in children. Two-hundred and seventeen children aged 6-12 years with acute cough who would normally be prescribed a cough mixture were enrolled in this study carried out in the General Practice setting. Children were randomised to receive one of two study medicines for 72 hours:

- Pholcolix linctus 5ml 4 times per day, containing
  - pholcodine 5 mg (cough suppressant)
  - paracetamol 150 mg (analgesic, antipyretic)
  - phenylpropanolamine 12.5 mg (sympathomimetic decongestant)
- Actifed linctus 7.5 ml 3 times per day, containing
  - codeine phosphate 10 mg (cough suppressant, analgesic)

- triprolidine hydrochloride 1.25 mg (antihistamine)
- pseudoephedrine hydrochloride 30mg (sympathomimetic decongestant)

The first dose was observed during the enrolment clinic visit. The investigator recorded the patient's initial assessment of palatability on a scale from *(-) unpleasant* to *(++) very pleasant*. Parents were given a diary card on which to record the doses taken, effectiveness and palatability.

At the second visit, parents were asked to return the bottle of medication. A final dose was given and palatability again recorded, the remaining volume was measured to assess compliance, and symptoms were re-evaluated to assess effectiveness. Parents were asked specifically about drowsiness, tremor, tachycardia, nausea and anorexia.

Of the 217 children who completed the study, 107 received Pholcolix and 110 received Actifed. Response to treatment is shown in Table 6 as the number of patients with symptoms at the second visit.

Both treatments were reported to produce highly significant ($p<0.001$) responses for productive cough and sore throat. There was also a highly significant response for other symptoms (predominantly headache, earache and catarrh) in the Pholcolix group, and a significant ($p<0.01$) improvement in dry cough in the Actifed group. Table 6

No side-effects were reported other than those specifically elicited. Overall, Actifed was associated with more side-effects than Pholcolix. Drowsiness was the most frequently reported side-effect, which was experienced by 59/110 in the Actifed group and 28/107 in the Pholcolix group. Two children were reported to have tremor and three children experienced heartburn in the Actifed group. Fourteen children in the Actifed group experienced nausea compared to 8 in the Pholcolix group, and anorexia was experienced by 8 children in each group. No children experienced tachycardia.

The authors concluded *'these data confirm the efficacy of both 'Pholcolix' and 'Actifed' Compound in children with acute cough, but the greater palatability and freedom from side-effects demonstrated for 'Pholcolix' would suggest that it is particularly useful in dealing with this very common problem.'*

Comments:

This study was aimed to assess which of two combination medicines for cough and cold symptoms was better tolerated in children aged 6-12 years.

The study has a number of flaws, including the lack of placebo arm, non-blinding of study medicine (different volumes and dose intervals), and an efficacy measure that is confounded by the natural course of the illness. (ie, acute upper respiratory tract infections get better on their own).

This study does not provide useful information on the efficacy of pholcodine or its effectiveness relative to codeine, as both medicines were given in combinations with other cough and cold medicines (a decongestant and either paracetamol or an antihistamine).

3.1.8 Belcher and Rees, 1986 (Thorax)

Effects of pholcodine and salbutamol on citric acid induced cough in normal subjects [13]

This randomised, double-blind, placebo-controlled, cross-over study compared the effectiveness of salbutamol and pholcodine on citric acid induced cough in 10 healthy, non-asthmatic volunteers. The subjects were all hospital staff or medical students at Guy's Hospital London where the research unit was based. All subjects were non-smokers and were not taking any other medicines.

On four days one week apart, at the same time of day, subjects received the following four combinations in randomised order:

- Placebo pholcodine and salbutamol 4 mg
- Pholcodine 10 mg and placebo salbutamol
- Pholcodine 10 mg and salbutamol 4 mg
- Placebo pholcodine and placebo salbutamol

Each medicine was formulated in a syrup and the dose administered was 10 ml.

Citric acid was given as three inhalations (2 minutes apart) of doubling concentrations of nebulised citric acid, beginning at 1.25% and ceasing when all three inhalations at one concentration produced an immediate cough, or at 80% citric acid. On each study day the citric acid cough threshold was measured, 10 ml of both test syrups were given and the threshold was measured again two hours later. Citric acid thresholds before and after each treatment were compared by the Wilcoxon matched pairs signed rank test.

Cough thresholds before and after the four treatments are shown in Table 7. There was considerable variation in pre-treatment cough thresholds between individuals, but for each individual the pre-treatment cough threshold was fairly consistent. One subject was excluded after developing an upper respiratory tract infection.

There were no significant differences between pre-treatment and post-treatment cough thresholds on placebo or salbutamol days. Administration of pholcodine was associated with a significant increase in cough threshold when given alone ($p<0.05$) or in combination with salbutamol ($p< 0.05$). The degree of change in threshold produced by pholcodine was not increased by combination with salbutamol.

[redacted]

The authors concluded: *'Our study has confirmed the effectiveness of pholcodine in the form, but failed to show an effect of oral salbutamol alone or as an addition to pholcodine. These findings relate only to acute, artificially induced cough in normal subjects. … Our results suggest that β stimulants are unlikely to be helpful in the suppression of cough in the absence of increased bronchial reactivity.*

Comments:
This study aimed to investigate the value of salbutamol as a cough suppressant by comparing it with both placebo and a 'positive control' pholcodine. The study is very small with data from just nine patients included in the analysis. It is not clear whether the efficacy results for pholcodine obtained in this healthy population with induced cough can be extrapolated to patients with acute non-productive cough of viral aetiology.

3.1.9 Equinozzi and Robuschi, 2006 (Treatments in Respiratory Medicine)

Comparative efficacy and tolerability of pholcodine and dextromethorphan in the management of patients with acute, non-productive cough. A randomised, double-blind, multicentre study. [14]

A copy of the published report was not available for this review. The information below is taken from the abstract and the published Clinical Trial Report[1].

This Phase 3 clinical trial was a multicentre, prospective, double-blind, randomised, active-controlled, parallel group study, performed in Italy in General Practice settings. The primary objective was to show that a 3-day treatment with pholcodine exhibits comparable efficacy, in terms of daytime cough frequency versus dextromethorphan in patients with acute non-productive cough. Secondary objectives included comparison of cough intensity and night-time symptoms between the two medicines, and a comparison of the incidence of adverse events.

The study enrolled 129 patients aged 18-70 years with acute non-productive cough with a frequency of daytime cough score ≥ 3 (on a 5-point scale) at baseline, and were otherwise healthy. Patients with cough for > 2 weeks, respiratory failure, bronchial hypersecretion, neoplasm, lower respiratory tract diseases, TB or asthma were excluded.

Patients were randomized to either pholcodine or dextromethorphan treatment for 3 days and were followed-up within 3 days from the last administration. The study drugs included:

- Pholcodine 19.65 mg (15 ml) three times per day
- Dextromethorphan 19.95 mg (15 ml) three times per day

[1] The Clinical Trial Report for this study is available at: https://www.clinicaltrialsregister.eu/ctr-search/trial/2004-000866-11/results (accessed 14-11-2019).

The study is described as a non-inferiority study. Sample size was calculated assuming that about 70% of the patients in each group improve their score by at least one point (corresponding to a 1 point decrease in the original five point rating scale). A minimum sample size of 56 patients in each group would provide 90% power.

A reduction of 1.4 (±0.9) and 1.3 (±0.8) points in the mean daytime cough frequency at day 3 was seen in the pholcodine and dextromethorphan groups, respectively, in the per-protocol population. The reduction in mean night-time cough was 1.3 for both groups. Cough intensity reduction was 0.7 for pholcodine and 0.8 for dextromethorphan.

Six of the 62 patients (9.7%) treated with pholcodine reported 8 adverse events, 4 of which (6.5%) were considered definitively, probably or possibly related to the treatment. One patient was permanently discontinued for 'emergent epigastralgia'. In the dextromethorphan group 11 of the 66 patients (16.7%) reported 19 adverse events, 11 of which (10.6%) were considered definitively, probably or possibly related to the treatment. Three patients were permanently discontinued for five emergent AEs (vomiting and vasovagal syncope, nausea and vomiting, asthenia and somnolence).

The investigators concluded that the efficacy of a 3-day course of pholcodine is similar to that of dextromethorphan in the treatment of adult patients with acute, non-productive cough. Both medicines were well tolerated.

Comments:

Industry funded study. No placebo arm. Study concludes that efficacy of a three-day course of pholcodine is similar to that of dextromethorphan in the treatment of adult patients with acute, non-productive cough. However, without a placebo control group, it is not possible to say whether any observed improvement was due to the medicine or spontaneous recovery form the short-term viral illness.

Table 8. Summary of pholcodine efficacy studies

Study [Ref.no]	Study type	Population	Study medicine	Frequency & Duration	Outcome measure	Efficacy	Adverse effects	Comment
Snell 1957 [6]	double-blind, semi-randomised, placebo- and active-controlled trial	45 adult patients (mix of in-patients and out-patients) with chronic bronchitis, 'pulmonary new growth', bronchiectasis, mitral stenosis or chronic pulmonary TB United Kingdom	Pholcodine 4mg + antazoline (antihistamine) + ipecac (expectorant) linctus Diamorphine (heroin) 6.4 mg linctus Placebo	Single dose at bedtime for 2 days per medicine (all three medicines administered over a 6 consecutive days.	Patient reported severity of cough between time of drug administration and sleep. Patients ranked each preparation in order of preference	No statistically significant difference between pholcodine and diamorphine ($p>0.05$), but both were superior to placebo.	Not reported	Analysis seriously flawed as patients who reported no difference between effectiveness of sequentially administered medicines were excluded. Contribution of antihistamine and expectorant to antitussive effect of pholcodine cannot be excluded. Analgesic, hypnotic and euphoric effects of heroin may also have influenced study measures.
Bickerman 1960 [7]	double-blind, self-controlled study comparing various drugs with placebo	16 healthy 'trained' volunteers with citric acid induced cough	13 drugs, including pholcodine 10 mg, codeine 10 mg and placebo	single dose	Cough frequency and intensity recorded by microphone and pneumotachograph.	Pholcodine 10 mg showed significant cough suppression over 4 hour test. Effect approximately equivalent to codeine 15 mg	not reported	Methodological study. No direct analysis of pholcodine vs placebo or vs codeine in individual subjects.
Heffron 1961 [8]	uncontrolled, non-blinded, observational study	54 prison inmates with cough of various aetiology and duration.	Pholcodine 5mg tablets, 1-2 tablets	up to four times per day for several days to 7 months,	Patient reported reduction in cough	15/19 patients with acute cough and 27/35 patients with chronid cought experienced reduction in cough with pholcodine in	Adverse effects including nausea, dyspepsia, flatulence,	Poor quality study, does not contribute meaningful evidence of efficacy

Study [Ref.no]	Study type	Population	Study medicine	Frequency & Duration	Outcome measure	Efficacy	Adverse effects	Comment
		United States		depending on response		doses ranging from 10 to 100 mg daily mg for periods of 2 days to 7 months	diarrhoea and anorexia reported in approximately one quarter of patients.	
Mulinos 1962 [9]	Not clear	23 adult in-patients with chronic cough due to pulmonary TB United States	Pholcodine 10-20 mg Codeine sulfate 10-20 mg Placebo	2-4 times per day for 1-29 days	Cough relief (not further defined)	Marked to complete cough relief: Pholcodine 16/16 (100%) Codeine 12/17 (70%) Placebo 4/18 (23%)		Small number of patients in each group. No statement on statistical significance
	Cross-over study	26 adult in-patients with chronic cough due to pulmonary TB United States	Pholcodine 10-20 mg Codeine sulfate 10-20 mg Placebo	Single dose at night, alternating between each drug, over a one week period.	Cough relief assessed by ward physician, and expression of preference for each drug by patient	Marked to complete cough relief: Pholcodine 10 mg 15/23 (65%) Pholcodine 20 mg 21/22 (95%) Codeine 10 mg 20/24 (83%) Codeine 20 mg 22/22 (100%) Placebo 24/47 (51%)		Contrary to authors' conclusion, overall, codeine appears to have greater efficacy than pholcodine as a cough suppressant. However, the number of patients in each group is small and there statistical significance not determined.
Rose 1967 [10]	Randomised, double-blind cross-over study	45 adult patients with 'some degree of chronic respiratory disease' in general practice setting. United Kingdom	Pholcodine 15mg + Pseudoephridrine hydrochloride 15 mg Codeine phosphate 60 mg	One month treatment at unspecified dose frequency not stated. One month	Severity of breathlessness and cough assessed by patient questionnaire and physician review at start of trial and	Pholcodine-pseudoephedrine linctus reported to improve cough and breathlessness significantly more than codeine.		Cause of cough not described, but 42/45 patients had both cough and breathlessness. No placebo arm.

Study [Ref.no]	Study type	Population	Study medicine	Frequency & Duration	Outcome measure	Efficacy	Adverse effects	Comment
					after each course of treatment.			Pholcodine given in combination with pseudoephedrine so unable to differentiate between the effects of each of these drugs Dose and frequency of administration not stated
Edwards 1977 [11]	Self-controlled, randomised, cross-over study	24 adult patients with productive cough due to chronic bronchitis seen in outpatient clinic. Patients admitted to hospital for duration of 5-day study. United Kingdom	Pholcodine 15mg + phenyltoloxamine 10 mg / 5 ml Pholcodine 15 mg/ 5ml (long-acting) Pholcodine 15 mg/ 5 ml (short-acting) Placebo	A different study medicine was administered as 5 ml twice a day on each of four consecutive days, in random sequence.	Mean cumulative cough bouts over 24 hours and total coughs in each 2-hour interval. Cough recorded using cough-actuated microphone.	Pholcodine + phenyltoloxamine was more effective than pholcodine alone (either resinated or unresinated) in reducing both bouts of coughing and total number of coughs.	Not reported	Efficacy of pholcodine in patients with productive cough from chronic bronchitis was not demonstrated.
Jaffé 1983 [12]	Non-blinded, parallel group	217 children aged 6-12 years with acute cough. General Practice setting. United Kingdom	Pholcolix linctus 5ml containing: pholcodine 5 mg, paracetamol 150 mg, and phenylpropanolamine 12.5 mg Actifed linctus 7.5 ml containing: codeine phosphate 10 mg, triprolidine	4 times per day for 72 hours 3 times per day for 72 hours	Palatability, compliance and effect on cough and sore throat	Significant improvement in productive cough, sore throat and other symptoms (headache, earache and catarrh) with Pholcolix.	Pholcolix associated with drowsiness (26.1%) nausea (7.5%) and anorexia (7.5%). Unclear how much the underlying illness and combination	Poor quality study of combination medicines (one of which contains pholcodine), no placebo arm and not blinded. Observed improvements with either medicine cannot be

Study [Ref.no]	Study type	Population	Study medicine	Frequency & Duration	Outcome measure	Efficacy	Adverse effects	Comment
			hydrochloride 1.25 mg and pseudoephedrine hydrochloride 30mg				medicines contributed.	differentiated from natural course of the underlying illness. The study does not contribute useful information on the efficacy of pholcodine
Belcher 1986 [13]	Self-controlled, cross-over study	Nine healthy volunteers. Citric acid induced cough United Kingdom	Placebo pholcodine and salbutamol 4 mg Pholcodine 10 mg and placebo salbutamol Pholcodine 10 mg and salbutamol 4 mg Placebo pholcodine and placebo salbutamol	Single dose of different study medicine on four days, one week apart	Change in threshold concentration (%) of citric acid required to induce cough following administration of study medicine	Significant increase in cough threshold when given alone or in combination with salbutamol, but no improvement with salbutamol alone or placebo.	Not reported	Small study. Not clear whether these results in healthy volunteers with induced cough can be extrapolated to patients with acute non-productive cough of viral aetiology.
Equinozzi 2006 [14]	Multicentre, randomised, parallel group, controlled, double-blind study.	Adult patients with acute, non-productive cough General Practice setting Italy	Pholcodine 19.65 mg Dextromethorphan 19.95 mg	3 times per day for 72 hours			Pholcodine generally well tolerated. Epigastric pain lead to treatment cessation in 1 of 62 patients treated with pholcodine.	

3.2 Safety

3.2.1 Literature

The following information is taken directly from the 2012 EMA Review [15]

Equinozzi and Robuschi (2006) [14]

The details of this study were described in section 3.1.9 above. Only 17 of the 129 patients reported adverse events: 6 patients with pholcodine and 11 patients with dextromethorphan. The most frequently reported adverse reactions with both pholcodine (4.8%) and dextromethorphan (7.6%) were related to the gastrointestinal system (upper abdominal pain, diarrhoea, dyspepsia, nausea and vomiting). No serious adverse events were reported and no adverse event required additional treatment. All were resolved within 2-3 days. Treatment was discontinued in one pholcodine patient due to upper abdominal pain and in three dextromethorphan recipients because of vasovagal syncope and vomiting (n=1), vomiting (n=1) and asthenia and somnolence (n=1). In the investigator-rated global tolerability scores, 45.2% and 31.3% of pholcodine and dextromethorphan recipients, respectively, were rated as 'excellent' and 1.6% and 3.1% were rated as 'poor'. Pholcodine had significantly better tolerability than dextromethorphan (OR 2.18; 95% CI 1.03, 4.63; p=0.041). There was no placebo control group included in this trial. The authors concluded that both dextrometorphan and pholcodine were well tolerated with a slightly lower incidence of adverse events with pholcodine than dextromatorphan.

Heffron (1961) [8]

Fifty four (54) male inmates ranging in age from 21 to 65 years were included in this study. Nineteen (19) of the patients suffered from acute cough. Among them, two patients complained of nausea, including one who refused medication after the second day. In the other, nausea subsided after the first day of therapy. A third patient reported a 'burning sensation' in chest and throat, not serious enough to interfere with therapy. Thirty-five (35) patients had chronic cough. Among them, complaints of side effects were more frequent but confined to the first days of treatment. These included 6 complaints of 'gas' and nausea, one of diarrhoea and anorexia and three of anorexia with 'gas' or nausea. None was sufficiently serious to warrant discontinuation of therapy. Several patients in both groups reported a slight tranquilizing effect. Treatment had to be stopped in 7 subjects, however these were all former narcotic addicts and 5 of the 7 had received 80 mg pholcodine or more per day over a 3 to 4 month period. No withdrawal effects were reported upon cessation of the treatment.

Mulinos (1962) [9]

In this study subjects used pholcodine at a dose of 10 or 20 mg, 2 to 4 times a day for up to 29 days. When pholcodine or codeine was swapped for the placebo, subjects did not report a desire for the previous medications. There were also no reports of withdrawal symptoms.

Rose (1967) [10]

The trial preparation contained 15 mg pholcodine and 60 mg pseudoephedrine per dose. The control preparation consisted of 15 mg of codeine phosphate per dose. A total of 45 patients took part in the trial, all with some degree of chronic respiratory disease. One patient complained only of breathlessness and two only of cough, whilst the remainder suffered to a greater or lesser extent from both. Each patient received each preparation for one month. Ten (10) patients experienced one or more side effects with the pholcodine preparation, including 6 reports of nausea, 2 of sleeplessness, 2 of constipation and one of bitter taste. Eight (8) patients had side effects on the control linctus, including one report of sleeplessness, 3 of nausea, 3 of constipation, one of chest pain and one of flatulent dyspepsia. The level of severity was not reported.

Kelly (1963) [16]

In this comparative single-blind study, 53 children between 8 months to 17 years with acute cough with upper respiratory infections as the underlying cause were treated with either pholcodine 5 mg or codeine 8 mg for 5 days approximately. One patient in the pholcodine group, a 10-year-old girl with influenza bereaving her

mother vomited when administered the first dose of medication. Medication was immediately discontinued. In the codeine group, 8 patients complained of mild constipation.

Jaffe and Grimshaw (1983) [12]

In a large trial of 217 children between 6 and 12 years old, a pholcodine-containing combination product (paracetamol 150 mg, pholcodine 5 mg, phenylpropanolamine 12.5 mg, per 5 ml) or another combination product not containing pholcodine (codeine phosphate 10 mg, triprolidine hydrochloride 1.25 mg, pseudoephedrine hydrochloride 30 mg, per 5 ml) were given for 3 days. The parents of the subjects were asked to record side effects such as drowsiness, tremor, tachycardia, nausea and anorexia. In the pholcodine group, 28 children reported drowsiness, 8 reported nausea and there were 8 cases of anorexia. Two children complained of tremor and 3 of heartburn, all 5 cases occurring in the codeine group. The most significant difference between the groups involved drowsiness, where there was higher incidence in children taking the codeine preparation (χ^2=16.67; p<0.001); in the pholcodine group, 74 (70.5%) children were free from side effects compared with 43 (39.4%) children in the codeine group. This difference was significant (χ^2=20.91; p<0.001).

No adverse events have been observed in study Edward and al (1977) which enrolled 24 patients with chronic bronchitis [11].

3.2.2 CARM data

As at 30 September 2019, the Centre for Adverse Reactions Monitoring (CARM) has received 51 adverse reaction reports in which a pholcodine-containing product was considered a suspect medicine. The pholcodine-containing product was the only suspect medicine in 40 of the reports and the only reported medicine in 26 reports. The pholcodine-containing product is recorded as 'pholcodine' (21 reports), Difflam lozenges (13), Duro-Tuss (13), Difflam anti-inflammatory throat spray (3) and Phensedyl (1).

Duro-Tuss is a brand name for various combination cough mixtures, some of which contain pholcodine. Medsafe has approved 23 different products that include 'Duro-Tuss' in the product name. Of these, only 10 products contain pholcodine either alone (5) or in combination (5) with other cough and cold medicines (including bromhexine, cethypyridinium, pseudoephedrine or phenylephrine). Similarly, there is a range of Difflam products available, some of which contain pholcodine. The CARM data does not differentiate between these products.

Due to the lack of certainty about the specific product that was reported, only the 21 reports in which pholcodine was specifically listed are reviewed here. Table 9.

The majority of these reports were for allergic-type reactions, including two reports of anaphylaxis.

Table 9. CARM case reports for pholcodine *(suspect medicine in bold)*

Report ID	Date	Age/Sex	Medicine(s)	Dose	Reactions(s)	Time to onset	Outcome at time of reporting
002896	Aug 1971	7m M	**Pholcodine** **Codeine** Acetylsalycylic acid Erythromycin estolate	[redacted] [redacted] [redacted] -	Hypoventilation Apnoea Hypotonia Miosis Restless	[redacted]	[redacted]
004285	Oct 1973	0 F	**Phenylzine** **Pholcodine** **Phenylephrine** **Chlorpheniramine**	[redacted] [redacted] [redacted] [redacted]	Headache Vomiting Abdominal pain Therapeutic response increased	[redacted]	[redacted]
006822	Oct 1977	69 F	**Pholcodine** Aminophylline **Methdilazine** Guaiphenesin	[redacted]	Face oedema Bronchospasm Rash	[redacted]	[redacted]
013928	Aug 1985	55 F	Cotrimoxizole **Pholcodine**	[redacted] [redacted]	Rash maculo-papular	[redacted]	[redacted]
018198	Dec 1988	28 F	**Pholcodine** Triphasil	[redacted] [redacted]	Urticaria Oedema	[redacted]	[redacted]
024434	Jun 1993	38 F	**Erythromycin ethylsuccinate** **Pholcodine**	[redacted] [redacted]	Rash erythematous Oedema periorbital	[redacted]	[redacted]
033581	Feb 1997	67 F	**Pholcodine**	[redacted]	Vomiting Diarrhoea Sweating increased Abdominal pain	[redacted]	[redacted]
033753	Feb 1997	28 M	**Pholcodine**	[redacted]	Vomiting	[redacted]	[redacted]
035772	Sep 1997	8m M	**Pholcodine**	[redacted]	Rash Oedema	[redacted]	[redacted]
039569	Oct 1998	40 F	**Pholcodine**	[redacted]	Vomiting Pruritis Flushing Bronchospasm	[redacted]	[redacted]
042742	Aug 1999	17 F	**Pholcodine** Paracetamol	[redacted] [redacted]	Face oedema Pruritis Flushing	[redacted]	[redacted]

043027	Nov 1999	37 F	**Pholcodine** **Ciprofloxacin** Triphasil	[redacted]	Taste loss Anosmia Vision abnormal	[redacted]	[redacted]
048326	Aug 2001	72 M	**Pholcodine**	[redacted]	Rash	[redacted]	[redacted]
051449	May 2002	24 F	**Pholcodine** Paracetamol	[redacted]	Palpitation Sleep disturbed	[redacted]	[redacted]
059934	Apr 2004	60 F	**Pholcodine**	[redacted]	Rash Pruritus	[redacted]	[redacted]
061462	Jul 2004	33 F	**Pholcodine**	[redacted]	Vision abnormal	[redacted]	[redacted]
068413	Sep 2005	- M	**Pholcodine**	[redacted]	Pruritus	[redacted]	[redacted]
084894	Jun 2009	43 M	**Pholcodine** **Amoxicillin/clavulanic acid** Menthol Eucalyptus	[redacted]	Angioedema Conjunctivitis Dizziness	[redacted]	[redacted]
086809	Oct 2009	21 M	**Pholcodine** **Codeine** **Morphine sulphate**		Allergy	-	[redacted]
114715	Dec 2014	63 F	**Pholcodine**	[redacted]	Anaphylactic reaction	[redacted]	[redacted]
118693	Nov 2015	69 F	**Pholcodine**		Anaphylactic reaction	[redacted]	[redacted]

3.3 Risk of anaphylaxis to neuromuscular blocking agents with prior exposure to pholcodine

3.3.1 Mechanism of IgE-mediated allergy

Anaphylaxis is a life-threatening, systemic immediate hypersensitivity reaction to an allergen, which may be ingested, inhaled or injected. Symptoms typically occur within 30 minutes of exposure (usually within 5 minutes). Classic anaphylaxis results from IgE-mediated mast cell and basophil degranulation releasing histamine and other mediators. Non IgE-mediated reactions (previously referred to as "anaphylactoid") are clinically identical but are induced by direct interaction of the allergen with the mast cells or basophils.

The IgE-mediated reaction occurs after exposure to an antigen (allergen) that stimulates the production of IgE antibodies by B cells. After the initial exposure, antibody concentrations decease, but allergen-specific IgE binds to high-affinity IgE (Fc-epsilon-RI) receptors on mast cells and basophils. If there is a subsequent exposure to the antigen, it interacts with any surface-bound IgE that is specific for that allergen. Certain allergens are able to interact with IgE molecules on two or more receptors of the cell surface to cause cross-linking, which in turn causes the receptors to become aggregated and initiate intracellular signalling. Allergens that are capable of cross-linking are either multivalent (having multiple identical sites for IgE antibody binding) or univalent (having multiple different sites for IgE antibody binding). If signalling is sufficiently robust, the mast cell (or basophil) becomes activated and degranulates, releasing preformed mediators, enzymes, and cytokines (such as histamine, tryptase, and tumor necrosis factor [TNF], respectively) and initiating additional mediator, cytokine, and enzyme production. These mediators either act directly on tissues to cause allergic symptoms or recruit and activate additional inflammatory cells, particularly eosinophils. The recruited cells, in turn, release more mediators and propagate a fulminant "chain reaction" of allergic inflammation. [17-20]

Intraoperative anaphylaxis is a relatively rare event, but it is nonetheless a significant problem as it may cause significant morbidity and has a mortality rate of 3.5-10%. The most common causes of intraoperative anaphylaxis are neuromuscular blocking agents (NMBAs), latex and antibiotics.

Evidence linking intraoperative anaphylaxis to neuromuscular blocking agents with prior exposure to pholcodine has emerged over the past 10-15 years. A summary of the evidence is presented below.

3.3.2 Incidence of anaphylaxis to NMBAs

The Royal College of Anaesthetists 6th National Audit Project on perioperative anaphylaxis in the United Kingdom reported that the overall incidence of reported NMBA-induced anaphylaxis was 5.3 per 100,000 exposures. Succinylcholine had the highest incidence (11.1 per 100,000 exposures) [21]. A total of 266 reports of intraoperative anaphylaxis were reported over a one-year period (2016) from all NHS hospitals in the UK. In 64 (25%) of these cases the trigger was identified as a NMBA, including rocuronium (42%), atracurium (35%), succinylcholine (22%) and mivacurium (1.5%). Table 10.

The incidence of anaphylaxis to NMBAs varies between countries. In 2000, the Norwegian Medicines Agency (Statens Legemiddelverk) issued a recommendation to Norwegian anaesthetists to stop using rocuronium in

routine anaesthetic practice [22]. The Agency had received 29 reports of anaphylaxis or anaphylactoid reactions to rocuronium over a two and a half year period in which approximately 150,000 patients had received the medicine. This number was significantly higher than in other Nordic countries, where a total of only seven cases of anaphylaxis had been recorded in approximately 800,000 patients administered rocuronium up to December 2000 (Table 11).

Although the reason for this discrepancy between Nordic countries was unclear, the apparent increase in anaphylactic reactions with rocuronium use in Norway was postulated to be due to differences in the reporting of anaphylaxis to NMBAs, and to statistical and methodological problems associated with rare adverse events (such as small sample size, skewed distribution of data and statistical variance) [22]. Marginal under-reporting has a disproportionately large effect on calculated incidence when the event being recorded occurs only very rarely [21].

In 2003, Mertes *et al* reported the results of a 2-year survey (January 1, 1999, and December 31, 2000) of anaphylactic (IgE mediated) or anaphylactoid (non IgE mediated) reactions occurring during anaesthesia in France. NMBAs were the most common cause of anaphylaxis (306/789, 58.2%), with rocuronium (43.1%) and succinylcholine (22.6%) the most frequently incriminated. [23]

In 2011, the same authors reported on an 8 year survey of anaphylaxis during anaesthesia in France from 1 January 1997 to 31 December 2004. Estimated incidence was obtained by combining survey data with data from the French pharmacovigilance system. Exposure data was obtained from data collected during a national survey of anaesthesia practice. A NMBA was the most common cause of IgE mediated reactions, occurring in 1067 of 1816 cases (58.8%). [24]

The incidence of IgE mediated anaphylaxis in Western Australia was estimated to be 2.8 and 8.0 per 100,000 exposures for vecuronium and rocuronium, respectively. Rocuronium was responsible for 56% of cases of NMBD anaphylaxis, succinylcholine 21%, and vecuronium 11%. [25]

In the 2012-2014 Triennial Report of the Victorian Consultative Council on Anaesthetic Mortality and Morbidity there were four deaths due to anaphylaxis (two suxamethonium, two rocuronium) and a total of 48 cases of anaphylaxis causing morbidity. More than half (25 case reports) were due to the administration of NMBAs, 13 cases were due to antibiotics and 10 due to other adjuvant agents [26].

Brusch et al [27] compared reported rates of anaesthetic-associated anaphylaxis in various countries and regions (Table 12), and noted that NMBAs account for 11% of anaesthesia-related reactions in the United States, compared to approximately 60% in Europe and Australia.

[redacted]

3.3.3 Role of the quaternary ammonium ion (QAI)

The molecular basis of anaphylaxis to NMBAs is recognition by IgE antibodies of tertiary or quaternary ammonium ions (QAI) present on all NMBAs, which also accounts for the allergenic cross-reactivity seen between NMBAs (Figure 2). The antibodies do not recognize primary and secondary amino groups. All NMBAs have at least two tertiary and/or quaternary ammonium ions. The distance between the ammonium ions is sufficient to bridge adjacent mast cell-bound IgE molecules, thereby inducing mast cell mediator release [28, 29]. Other amines, including tertiary structures have also been shown to function as haptens and to inhibit the QAI-specific reaction [30].

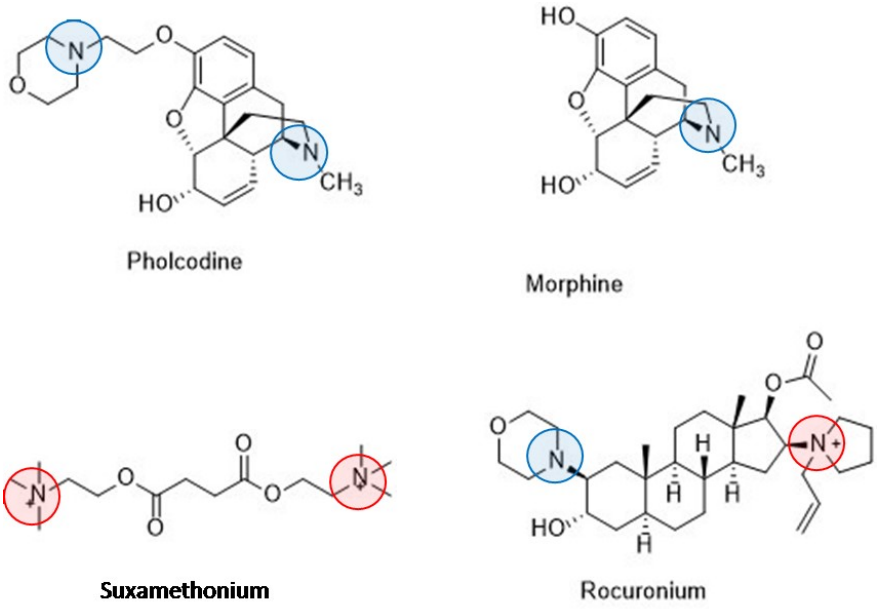


Figure 6. Molecular structures of pholcodine, morphine, suxamethonium and rocuronium
Tertiary ammonium structures highlighted in blue, quaternary ammonium ion highlighted in red

The majority of patients who experience anaphylaxis to a NMBA have not had prior exposure to any drug of this class. As prior exposure is a prerequisite for IgE-mediated anaphylaxis, these patients must have been exposed to a molecule with cross-reactivity to the allergenic component of the NMBA.

Since compounds containing tertiary and/or quaternary ammonium groups occur widely in the human environment in drugs, cosmetics, disinfectants, industrial materials, foods, etc. it has been suggested that

sensitization to NMBDs may occur via these sources and this could explain the lack of previous exposure seen in many of the anaphylactic patients [28].

Currently-used NMBAs are either monoquaternary (vecuronium and rocuronium) or bisquaternary (suxamethonium, atracurium, mivacurium, pancuronium). There is no evidence that the risk of anaphylaxis is related to the number of quaternary ammonium groups. Individuals may be allergic to more than one NMBA [31]. Cross-sensitivity (based on skin testing and specific IgE) is common, with suxamethonium being the most commonly cross-reacting drug [25]. Cross-sensitivity may occur between different classes of NMBA as well as within classes.

3.3.4 The pholcodine hypothesis

The pholcodine hypothesis holds that widespread use of pholcodine is responsible for a higher risk of anaphylaxis to NMBDs due to similarities in their structures. The evidence in support of this hypothesis is presented below.

3.3.4.1 Florvaag, Johansson, et al, 2005 (Acta Anaessiological Scandinavica)

Prevalence of IgE antibodies to morphine. Relation to the high and low incidences of NMBA anaphylaxis in Norway and Sweden, respectively [32]

Following publication of reports that anaphylactic reactions to NMBAs were more than six times more common in Norway than in Sweden, Florvaag *et al* undertook a study to document the prevalence of IgE sensitisation to NMBAs in each county. Mertes *et al* had previously noted that up to half of patients with anaphylaxis to an NMBA had no prior exposure to any NMBA, suggesting that other drugs or environmental substances with the same allergenic epitope as NMBAs may have led to sensitisation [33]. This study therefore aimed to explore whether various household and environmental chemicals may have caused sensitisation to NMBAs.

Serum samples left over from diagnostic testing for IgE antibodies were obtained from the allergy diagnostic laboratories in Bergen (301 samples) and Stockholm (300 samples). The samples were collected consecutively during March-April 2002. Samples from 500 blood donors in both Bergen and Stockholm were also tested. These 'Allergic' and 'Donor' serum samples were compared with serum samples from 65 Norwegian patients (approx. 2/3 women) with a documented NMBA-induced anaphylactic reaction during anaesthesia ('Anaphylactics'). The samples were tested for IgE antibodies to morphine and suxamethonium using Phadia ImmunoCAP® (Uppsala, Sweden), a solid-phase immunoassay[2]. Suxamethonium was selected as it was said to exemplify NMBAs.

In addition, 84 household and other environmental chemicals were collected from the homes of both sensitised and non-sensitised individuals in Bergen and Stockholm in an effort to identify possible environmental factors that might explain the geographical differences in the prevalence of sensitization. Substances known to contain the quaternary amine ion were a particular focus. The presence of morphine and suxamethonium reactivity was studied using IgE antibody inhibition analyses on pooled sera with IgE antibodies to the morphine or suxamethonium allergens, respectively.

Of the 65 Norwegian 'Anaphylactics', 44 (67.7%) were sensitized to morphine but only 25 (38.5%) had IgE antibodies to suxamethonium (Table 13).

Among the 'Allergic' samples, none of the 300 sera from Stockholm had antibodies to morphine or suxamethonium. Thirty of 301 (10%) serum samples from Bergen were positive to morphine, of which 11 were positive and 19 were negative to suxamethonium. Two sera from Bergen were positive to suxamethonium and negative to morphine, but the reaction to suxamethonium could be inhibited by morphine. The majority of sensitised individuals were women (22/32; 69%). (Table 13)

[2] Information on the Phadia ImmunoCAP test is available at: http://www.phadia.com/en/Products/Allergy-testing-products/ImmunoCAP-Lab-Tests/sIgE/Test-Principle/ (accessed 20 Nov 2019).

Among the 'Donor' samples, none of the 500 sera from Stockholm had antibodies to morphine or suxamethonium. Twenty-five of the 500 (5%) serum samples from Bergen had IgE antibodies to morphine but only two (0.4%) to suxamethonium. Among the positive donors there was a slight over-representation of women (6.6%) for morphine compared to men (3.4%). (Table 13)

Of the 84 samples of environmental chemicals, 43 had a positive reaction for morphine IgE antibody inhibition and 34 had positive reaction for suxamethonium IgE antibody inhibition (Table 14).

No difference was found between Norway and Sweden regarding environmental exposure to most of these chemicals, with the exception of cough syrups. Differences in cough syrup availability and per capita sale are shown in Table 15.

IgE antibodies to pholcodine were subsequently tested and were found to be present in 6.0% of blood donors from Norway and in no serum from Sweden (Table 13). At this stage in the study there were no remaining serum samples from 'Allergics' for testing IgE antibodies to pholcodine.

To characterise the allergenic epitopes of morphine and suxamethonium, cross-inhibitions using morphine and choline were performed on eight sera with different patterns of IgE antibodies to morphine and suxamethonium. The results indicated that morphine has at least two non-cross reacting allergenic epitopes, one of which is shared by suxamethonium. The latter is most likely the QAI-related allergen, while the former does not appear to be shared by the NMBAs.

When comparing the allergenic characteristics of morphine and pholcodine, there was significant correlation between the presence of IgE antibodies to morphine and pholcodine in sera from anaphylaxis patients and from blood donors. Of the sera positive to morphine, 21/32 (66%) of the 'Allergics' and 23/25 (92%) of the 'Donors' were negative to suxamethonium. Of the sera negative to morphine, 2/32 of the 'allergic' and none of the 'donors' were positive to suxamethonium.

Key findings from this study were that none of the sera tested from Sweden were positive for IgE antibodies to morphine or suxamethonium. The majority of those sensitised were women. Several household chemicals exhibited suxamethonium and/or morphine activity, but the only difference between Norway and Sweden was cough mixtures containing pholcodine. IgE antibodies to pholcodine were found to be present in 6.0% of blood donors from Norway but in no serum from Sweden. The authors considered that a possible explanation for the geographic differences in IgE sensitisation to morphine, suxamethonium and pholcodine between Bergen and Stockholm was the unrestricted use of cough mixtures containing morphine derivatives, particularly pholcodine, in Norway.

Comments:

This study compared sera from Norwegian and Swedish blood donors and patients with suspected allergy (samples from allergy diagnostic clinic), and Norwegian patients with documented NMBA-initiated anaphylaxis.

In Norway 0.4% of blood donors, 3.7% of 'allergics' and 38.5% of 'anaphylactics' were IgE-sensitized to suxamethonium, and 5.0%, 10.0% and 66.7%, respectively, to morphine. None of the sera from Sweden were positive.

The sera were initially tested against IgE antibodies to morphine and suxamethonium. Morphine was used as a control, as it was considered to be a substitute for detecting IgE-sensitisation to the QAI (ie, morphine was used as a substitute for testing against all NMBAs, some of which had proven difficult to formulated in a test solution) [32]. However, the presence of IgE antibodies to morphine was found to have a low specificity for IgE-sensitization to suxamethonium.

Since major differences in prevalence of sensitization between Bergen and Stockholm were found, attempts were made to identify factors in the environment that might explain the geographical differences. The sera

were therefore tested against 84 house-hold chemicals and medicines, focusing particularly on those with a QAI structure.

Among the environmental substances, 43 were positive to morphine and 34 were positive to suxamethonium. The only differences observed between the two countries were in cough mixtures containing pholcodine. This finding initiated the so-called 'pholcodine hypothesis'.

The finding that 69% of the Norwegian samples taken from 'Allergics' were female may reflect higher sensitisation to environmental substances that share the QAI, however, it may be due to selection bias. The samples came from an allergy testing clinic. As women more frequently engage with health services, women are also likely to be over-represented in the population referred to allergy testing. The paper does not report the proportion of 'Allergic' or 'Donor' serum samples that were from women, (but does note that 2/3 'Anaphylactis' were women).

3.3.4.2 Florvaag, Johansson, et al, 2006 (Allergy)

Pholcodine stimulates a dramatic increase of IgE in IgE-sensitized individuals. A pilot study [34]

Following on from their previous study [32], the authors explored the effect of pholcodine cough mixture on IgE production in four individuals sensitised from previous exposure to pholcodine and in two non-sensitised individuals.

Serum concentrations of IgE and IgE antibodies to pholcodine, morphine and suxamethonium allergens (ImmunoCAP®) were measured after intake of pholcodine cough syrup, or exposure to confectionary and other household chemicals containing various amounts of substances cross-reacting with pholcodine, morphine and suxamethonium.

The authors reported that cough syrup containing pholcodine resulted in a 60-105 times increase in IgE and a 30-80 times increase in IgE antibodies to pholcodine, morphine and suxamethonium, within 1-2 weeks in sensitised individuals. Of the two sensitised individuals exposed to pholcodine, one experience severe pruritus and the other developed urticaria, both responding to antihistamines. The tested confectionary did not have any similar stimulating effect, but seemed to counteract the expected decrease of IgE. No effect was seen in non-sensitised individuals.

The authors concluded *'It seems as cough syrups containing pholcodine had a most remarkable IgE boosting effect in persons IgE-sensitized to PHO, MOR and SUX related allergens. Household chemicals containing such allergenic epitopes seem capable of some, minor, stimulation'*.

Comments:

The study is very small. It includes the authors as participants and a handful of patients from an allergy clinic in Bergen. The study protocol is not clear from the paper. Blood sampling from each individual appears to have taken place at inconsistent time intervals after the exposures.

3.3.4.3 Harboe, Johansson, et al, 2007 (Allergy)

Pholcodine exposure raises serum IgE in patients with previous anaphylaxis to neuromuscular blocking agents [35]

Following on from the pilot study described above, the same research group aimed to explore the effect of pholcodine exposure on IgE in a population with previously diagnosed IgE-mediated anaphylaxis to NMBAs.

Seventeen patients were randomized to take cough syrup containing either pholcodine (n=11) or guaifenesin (n=6) for one week. The dose administered was 10 ml once daily for both medicines.

Total serum IgE and specific IgE antibodies to pholcodine, morphine and suxamethonium were measured before and at 4 and 8 weeks after the start of exposure.

All patients completed the study protocol. One patient assigned to pholcodine experienced swollen eyelids during the last 3 days of cough syrup exposure.

There were no significant differences between the study groups in the concentrations of total IgE or IgE antibodies to pholcodine, morphine or suxamethonium prior to cough syrup exposure. At 4 weeks, there was a large increase in IgE concentration in the pholcodine group, which by 8 weeks had moderately declined (Table 16). No changes were seen in the guaifenesin group at either 4 or 8 weeks. IgE antibodies to inhaled and food allergens showed only slight elevation. The differences between the two study groups for all primary variables (IgE and IgE antibodies to pholcodine, morphine and suxamethonium) were highly significant ($p<0.01$).

The authors concluded that serum levels of IgE antibodies associated with allergy to NMBAs increase significantly in sensitized patients after exposure to cough syrup containing pholcodine, and called for the availability of pholcodine to be restricted because of the potential risk of future allergic reactions to muscle relaxants.

Comments:

This study is small, with only 11 and 6 patients in the pholcodine and guaifenesin groups, respectively. All of the patients had previously experienced NMBA-induced anaphylaxis. The study compares total IgE levels and IgE levels to pholcodine, morphine and suxamethonium before and after one week of exposure to either pholcodine or guaifenesin. The results are significant, and the difference in response to IgE levels between the two groups is striking.

A larger study with controls including participants without a prior history of anaphylaxis to NMBAs and those without prior exposure to pholcodine as a control would be useful.

It is interesting that only one patient experienced what appears to be an allergic reaction to the pholcodine, despite the shared allergenic epitope to NMBAs to which the patient had previously reacted.

3.3.4.4 Johansson, Öman, et al, 2009 (Allergy)

Pholcodine caused anaphylaxis in Sweden 30 years ago [36]

In this letter to the editor, the authors note that a cough mixture containing pholcodine, called Tussokon, was available on prescription in Sweden in the 1970s and 1980s. Tussokon 10 mg tablets were withdrawn from the market on 1 August 1985 and the 2 mg/ml pholcodine syrup was withdrawn on 1 July 1989. The products were withdrawn because of changes in recommendations for treatment of cough and because other, more effective pharmacological preparations had become available. There were no concerns at the time of a possible association with anaphylaxis during anaesthesia.

The mean pholcodine consumption in Sweden was highest during the 1970s, but had dropped to less than half in the 1980s. The cumulative number of reports of anaphylaxis was 4.5 per million in the 1970s, and 1.8 per million the following decade. No cases of anaphylaxis were reported after 1990 (Table 17) when pholcodine was no longer on the market.

The authors had access to frozen serum samples collected between 1970 and 1999 from patients selected for an IgE-mediated allergy. The sera were analysed for IgE antibodies to morphine, pholcodine and suxamethonium, using the same technique as in the previous studies. The percentage of sera with IgE antibodies to pholcodine and morphine dropped from the 1970s to the 1990s, and antibodies to suxamethonium dropped from the 1980s (Table 17). The small sample size for the 1970s and selected population are noted as limitations. The authors concluded that these results lend support to the pholcodine hypothesis.

Comments:

The percentage of samples with antibodies to pholcodine and morphine dropped from the 1970s to the 1990s, but it should be noted that the percentage of samples with antibodies to suxamethonium actually increased from the 1970s to the 1980s, and was still higher in the 1990s than for the 1970s. However, the small number of available samples from the 1970s may have contributed to the differences observed.

The number of reports of anaphylaxis during anaesthesia (any cause) in Sweden during the 1970s dropped to less than half in the 1980s. Although this may be attributable to the withdrawal of pholcodine from the market in the mid-late 1980s, the authors do not explore other potentially contributing factors that may have changed in the intervening years. For example, changes in reporting rates, patterns of use of other substances in the operating theatre (eg, antibiotics, latex), and demographic changes in the population.

Tussokon syrup was still available until 1989, so it would appear that the association, if real, between Tussokon and anaphylaxis during anaesthesia could only be with the pholcodine tablets rather than the syrup, as the number of reports dropped to less than half while the syrup was still available. However, the authors do not report on the relative usage of Tussokon in tablet or syrup formulation.

3.3.4.5 Johansson, Florvaag, et al, 2010 (Allergy)

National pholcodine consumption and prevalence of IgE-sensitization: A multicentre study [37]

This international, multi-centre study compared the prevalence of IgE antibodies to pholcodine, morphine and suxamethonium in serum from atopic individuals attending allergy centres or diagnostic laboratories in nine high or low pholcodine-consuming nations. IgE antibiodies to P-aminophenylphosphoryl-choline (PAPPC) were also measured to detect IgE sensitisation to QAI.

Serum was collected from the collaborating centres in Stockholm (Sweden), Bergen (Norway), Copenhagen (Denmark), Helsinki (Finland), Nancy (France), Manchester (UK), Rotterdam (The Netherlands), Freiburg

(Germany) and Lenexa, KS (USA), during 2005-2007. Serum concentrations of IgE and specific IgE antibodies to a mix of common inhalant allergens, and to pholcodine, morphine, suxamethonium and PAPPC were measured.

Data on national pholcodine consumption for 2001-2005 was obtained from the United National International Narcotics Control Board database. Arbitrary levels were chosen for high (> 100 kg per million inhabitants) and low (< 40 kg) pholcodine consumption. The number of pholcodine-containing drugs available in 2005 in the individual nation markets was obtained from Drugdex. No information was available on the number of individual exposed to pholcodine either in the general population or among the individuals who donated serum samples.

A sample size of approximately 200 sera collected at each of nine centres representing high and low consumption countries would yield a statistical power sufficient to test the null hypothesis: no difference in pholcodine sensitisation between high and low pholcodine consumption countries.

Pholcodine consumption in the nine participating countries varied from 0 to 184.9 kg per million inhabitants, with France, where 14 different pholcodine-containing drugs were available, having the highest level of consumption (Table 18).

The percentages of atopic individuals IgE-sensitised to pholcodine, morphine and suxamethonium varied from < 1% in low consumption countries (Denmark, Finland, Germany and Sweden) to 2.4-7.0% in high consumption countries (France, Norway and the UK). As expected from the high level of consumption, France had a high percentage of pholcodine sensitisation (6%); however, Norway had the highest proportion of sera with positive IgE antibodies to pholcodine, despite usage being only ~60% of that in France. (Table 19)

Samples from the US and Netherlands had a surprisingly high prevalence of IgE antibodies to pholcodine, 2.0% and 4.9%, respectively, but differed considerably for suxamethonium at 2.5% and 0%, respectively. The authors note these findings do not fit with the pholcodine hypothesis, and one explanation could be that other, yet unknown, environmental factors besides pholcodine may lead to production of IgE antibodies to pholcodine and suxamethonium. The presence of other, so far unknown sensitizers is further supported by the discrepancy between the Netherlands and the US regarding IgE antibodies to suxamethonium.

IgE sensitisation to PAPPC was unrelated to pholcodine consumption, indicating that this substance is not useful for detection of IgE sensitisation to QAI, although it contains the QAI structure.

The authors note that the relation between pholcodine consumption and exposure must be viewed with caution. The INCB data represents amounts of pholcodine officially purchased by the individual nations, but does not necessarily reflect exposure of the general population. Furthermore, it is not known how many of the anonymous allergic serum donors had actually been exposed to pholcodine.

Comments:

The United States, which had no pholcodine products on the market, was reported to have zero consumption per million inhabitants. In contrast, The Netherlands, which also had no marketed pholcodine products, did have some consumption of pholcodine, perhaps due to ease of access to cross-border medicines within the EU. However, despite the absence of pholcodine from the US market, and the classification of pholcodine in the US as a Schedule 1 Controlled Drug, 2% of the sera collected from the US had positive IgE antibodies to pholcodine.

This unexpected result raises questions about the specificity of the pholcodine IgE, accuracy of the test, and validity of the exposure data. Furthermore, the results are inconsistent with the pholcodine hypothesis.

3.3.4.6 Florvaag, Johansson, et al, 2011 (Allergy)

IgE-sensitization to the cough suppressant pholcodine and the effects of its withdrawal from the Norwegian market [38]

Following the withdrawal of pholcodine from the Norwegian market in March 2007, the authors examined the effect on total IgE and IgE antibodies to pholcodine, morphine and suxamethonium in serum samples from an allergy clinic in Norway, and on the frequency of anaphylaxis during anaesthesia.

Serum samples left over from allergy testing were again collected from the Allergy Section of the Laboratory of Clinical Biochemistry, Haukeland University Hospital, Bergen. Samples were allocated to three groups:

- Group A 'Allergics' – consisted of 301 consecutive samples collected without knowledge of clinical data or IgE levels, but with a residual volume of ≥ 350 µL *(this data was obtained during an earlier study by the same research group [32])*
- Group M (Medium) 'Allergics' – consisted of 100 sera with IgE levels between 1000 and 5000 kU/L
- Group H (High) 'Allergics' – consisted of 49 sera with IgE levels > 5000 kU/L.

Sampling was performed during April to June each year.

In addition, the authors compared the results of all IgE analyses performed at the laboratory in the 12 months preceding withdrawal of pholcodine ('Before', n = 24096), with results obtained during the following 12-month periods of 2007 ('1 year', n = 24129), 2008 ('2 years', n = 25806) and 2009 ('3 years', n = 26491).

Anaphylaxis reporting information was obtained from the Norwegian Network for Anaphylaxis during Anaesthesia (NARA, Haukeland University Hospital, Bergen) – a spontaneous reporting system with standardised clinical reaction data and sera collected at the time of suspected reactions.

IgE sensitisation in the three sub-populations of 'Allergics' was compared to levels in samples obtained from blood donors ('Donors') in the authors' previous study from 2005 [32]. Table 20

The prevalence of IgE sensitisation to pholcodine before and after removal of Tuxi® from the market is presented in Table 21. The 'before' data comes from the earlier study in 2005. By one year after pholcodine market withdrawal, IgE antibodies to pholcodine and suxamethonium reduced from 11.0% to 5.0% and from 3.7% to 0.7%, respectively. At three years, suxamethonium sensitization had continued to fall to 0.3%, pholcodine to 2.7% and morphine to 1.3%. All the changes were statistically significant ($p < 0.001$).

A significant decrease in the prevalence of elevated IgE was seen for the 120 kU/L cut point at 2 and 3 years after pholcodine withdrawal (Table 22) with a significant downward trend observed over the 4-year period (adjusted RR 0.81, p=0.001).

The incidence of reported suspected anaesthetic anaphylaxis fell significantly by 3 years after withdrawal of pholcodine (Table 23). The decrease was seen in both the total number of reported incidents and the number of reports in which an NMBA was used. A similar and statistically significant trend was seen for the total number of sera with IgE antibodies to SUX at the time of reaction, decreasing in 2009 to three and in the first 6 months of 2010 to two cases.

The authors concluded that the withdrawal of pholcodine from the Norwegian market significantly lowered levels of IgE and IgE antibodies to PHO, MOR and SUX, within 1-2 years, and, within 3 years had lowered the frequency of NMBA suspected anaphylaxis.

Comments:

The results presented in this paper are confusing. The authors state that the analyses presented in Table 20 were performed during the final years before the pholcodine-containing medicine Tuxi was withdrawn from the Norwegian market. However, Table 20 includes data from samples for 'Donors*' and Group A* 'Allergics' that were collected for the original study in 2005 [32], prior to the March 2007 withdrawal of pholcodine, and data for the Group M and Group H 'Allergics', which was collected for the current study 'during the months of April to June each year'. It is not clear exactly when the Group M and Group H samples were collected, what proportion preceded the withdrawal of pholcodine, or how this data was used in the study.

Table 21 presents the prevalence of IgE sensitisation to pholcodine, morphine and suxamethonium in the three groups of 'Allergics' sampled yearly up to three years after withdrawal of pholcodine. IgE to pholcodine was positive in 11% of samples before withdrawal, and then in 5.0%, 5.7% and 2.7% of samples at 1, 2 and 3 years after withdrawal, respectively.

However, also of note is a similar reduction in IgE sensitisation to morphine: 10% before, 2.7% at 2 years and 1.3% at 3 years. This reduction may have occurred due to the reduced exposure to pholcodine as they

both share the tertiary ammonium ion, but it would be interesting to know whether there was a corresponding reduction in allergic reactions to morphine during this time.

Table 22 shows a downward trend in the proportion of tests for total IgE that were found to be positive (ie, IgE >120ku/l) in the 12-month periods from 2006 (25.3%) to 2009 (21.5%).

Table 23 shows that both the total number of reports of anaphylaxis and the number that reported use of an NMBA dropped over the period 2005-2009. The proportion of cases with IgE to suxamethonium remained relatively stable (19.3-29%) until 2008, then dropped to 9% in 2009 and 11% for the first half of 2010. This reduction in IgE-suxamethonium indicates a reduction in the proportion of cases that were in fact caused by an NMBA (as IgE-suxamethonium indicates allergy to the QAI, which is the same for all NMBAs).

This data supports the pholcodine hypothesis in that the proportion of NMBA-anaphylactic cases that were in fact due to the NMBA dropped following withdrawal of pholcodine from the market in Norway.

NARA is a spontaneous reporting programme for anaphylaxis in anaesthesia. It is likely to be subjected to the same limitations of any spontaneous reporting programme for adverse events, particularly under-reporting and reporting bias. Following the withdrawal of pholcodine, which was widely held to be responsible for anaphylaxis to NMBAs, it is possible that the impetus to report may have decreased. Hence, the decline in reports by 2009-2010 may represent under-reporting due to a possible loss of interest in the issue among anaesthetists in Norway.

3.3.4.7 Johansson, Öman, et al, 2012 (Acta Anaesthesiologica Scandinavica)

Anaphylaxis to atracurium – a non-QAI-dependent reaction? [39]

In this Letter to the Editor the authors put forward a hypothesis that allergic anaphylaxis to the NMBA atracurium is unrelated to the classical QAI allergen.

This hypothesis is based on four case reports of anaphylaxis to atracurium in Sweden, in which none was IgE sensitised to morphine, pholcodine or suxamethonium. One case had a positive basophil test (basophil allergen threshold sensitivity) to atracurium but was negative to the other NMBAs. Serological testing with ImmunoCAP showed that two of the four patients had IgE antibodies to atracurium. The IgE binding could be completely inhibited by atracurium, but not by the other six NMBAs or by pholcodine. Table 24

Sera from three previously reported cases [40] with suxamethonium induced anaphylaxis with IgE antibodies to suxamethonium did not react to the atrcurium ImmunoCAP.

These cases indicate that anaphylaxis to atracurium is IgE antibody mediated but the nature of the allergen is not clear. If it is QAI, the epitope must be exposed in a unique way. As pholcodine is not present in Sweden, some other sensitizer must be involved. Since the two IgE-sensitised patients have had multiple operations, they may have been sensitised by repeated exposure to atracurium, although the number of previous exposures to the drug is not known.

The cases suggest that pholcodine exposure may not be of importance in anaphylaxis to atracurium. It is possible that repeated atracurium exposure during anaesthesia can induce the IgE sensitisation, but booster stimulation by pholcodine-related 'household' chemicals containing the atracurium allergen, e.g., cosmetics, cannot be excluded.

Comments:

This is a small case series by the same research group (the proponents of the pholcodine hypothesis). In this study, the authors propose another mechanism for sensitisation to the NMBA atracurium that does not involve pholcodine, and raise the possibility of other environmental sensitizers – a possibility that the group has not further explored.

3.3.4.8 Dong, Acouetey, et al, 2013 (Clinical and Experimental Allergy)

Prevalence of IgE against neuromuscular blocking agent in hairdressers and bakers [41]

This French study investigated the prevalence of specific IgE to QAI in two populations professionally exposed to QAI compounds. In a retrospective follow-up design, apprentices were assessed after their 2-year training period. Hairdressers (n=128) were compared with baker/pastry makers (n=108) and non-exposed matched control subjects from the sales or food sectors (n=379). All participants had recently graduated from one of nine vocational schools in the North of France. Participants were included if they had no previous anaesthesia, allergy manifestation or asthma, and they had not taken pholcodine during the 2-year training period.

A 4.6-fold higher frequency of positive IgE against QAIs was observed in hairdressers compared with baker/pastry makers and control groups. Competitive inhibition of quaternary ammonium Sepharose radioimmunoassay (QAS-IgE RIA) with succinylcholine was significantly higher in hairdressers (66.2% ± 7.4%), compared with baker/pastry makers (39.7% ± 6.0%) and control groups (43.8% ± 9.9%), $p < 0.001$. The specific IgE against QAI recognized two compounds widely used by hairdressers, benzalkonium chloride (present in shampoos) and polyquaternium-10 (present in shampoos and conditioners), in competitive inhibition of IgE RIA.

When considering the whole study population, hairdresser professional exposure and total IgE > 100 kU/L were the two significant predictors of IgE-sensitization against quaternary ammonium ions in the multivariate analysis that included age, sex, professional exposure, increased concentration of total IgE (IgE > 100 kU/L) and positive IgE against prevalent allergens (Phadiatop®; P = 0.019 and P = 0.001, respectively).

The authors concluded that professional hairdressing occupational exposure increases IgE-sensitization to NMBAs and quaternary ammonium ion compounds used in hairdressing. Besides the pholcodine hypothesis, repetitive exposure to quaternary ammonium compounds used in hairdressing is a risk factor for NMBAs sensitization.

Comments:

The study compared recently graduated hairdressers with known professional exposure to QAIs to other professional groups with less (bakers/pastry makers) or no known professional exposure. The study was retrospective, so no baseline measures were available from before they were exposed.

The main finding was the higher frequency of positive IgE against QAIs in hairdresser apprentices, compared with other apprentices, in the context of a 2-year high rate of professional exposure to cosmetics and absence of reported exposure to pholcodine and anaesthetics.

3.3.4.9 Katelaris, Kurosawa, et al, 2014 (Asia Pacific Allergy)

Pholcodine consumption and immunoglobulin-E sensitization in atopics from Australia, Korea, and Japan [42]

In a study, similar to that undertaken by Johansson et al in 2010 [37], the authors compared levels of IgE sensitisation in Australia (a high pholcodine-consumption country), Japan and the Republic of Korea (both low pholcodine-consumption countries).

Serum was collected at the collaborating centres in each country either as superfluous volumes from routine allergy laboratories (Japan and Korea), or were drawn from patients referred for allergy testing at a referral allergy centre (Australia). Sera were collected during the years of 2009–2012. Inclusion criteria were available serum volumes of at least 1.0 mL, a positive Phadiatop test or skin prick test to a panel of common inhalant allergens, and an IgE level below 10,000 kU/L or a Phadiatop® below 120 kUA/L if no IgE-value was available.

Each serum sample was tested for IgE (kU/L), IgE-antibodies (kU_A/L) to a mix of common inhalant allergens, Phadiatop®, and for IgE-antibodies to pholcodine, morphine, and suxamethonium by ImmunoCAP® Specific IgE, using 0.35 kU_A/L as the cut-off for a positive test.

Data on the national pholcodine consumptions summarized for the years 2008–2010 were taken from the United Nations International Narcotics Control Board database (www.incb.org).

Serum samples from Australia (93), Japan (134) and Korea (200) were tested for IgE-antibodies to pholcodine, morphine and suxamethonium. The percentage of samples with positive antibodies was higher in Australia than Japan and Korea for each substance (Table 25).

Of the 4 suxamethonium-positive sera in Australia, all were positive to pholcodine. In contrast, the one serum from Korea that was positive to suxamethonium was not positive to pholcodine, as were both of the Japanese samples (Table 26). Of the 8 morphine-positive sera in Australia, only 4 were positive to suxamethonium.

Pholcodine consumption in Australia was high (22.0 kg per million inhabitants per year), whereas in Japan and Korea no pholcodine-containing cough syrups were available. In the Australian study population 53 of 93 (57%) patients from whom samples were drawn indicated that they were frequent consumers of such cough mixtures.

Comments:

This study, which includes authors from the Norwegian research group, was undertaken to see whether the association between pholcodine exposure and IgE sensitisation to QAI observed in Sweden and Norway could be replicated in other countries with high and low pholcodine consumption, respectively

The study showed that in Australia where pholcodine is readily available, a higher proportion of serum samples (from allergy clinic attendees) had antibodies to suxamethonium and pholcodine compared to very few in countries where these medicines are not available.

However, despite pholcodine not being available in Japan and Korea, approximately 1% of samples from each country had antibodies to pholcodine. This observation was not discussed further.

The samples sizes for each country are relatively small and statistical significance is not reported.

3.3.4.10 De Pater, Florvaag, et al, 2017 (Allergy)

Six years without pholcodine; Norwegians are significantly less IgE-sensitized and clinically more tolerant to neuromuscular blocking agents [43]

This study examines reports to the Norwegian Network for Anaphylaxis under Anaesthesia (NARA) 6 years after pholcodine was withdrawn from the Norwegian market.

Since 1997, NARA has collected standardized data on suspected anaphylactic reactions during general anaesthesia.

At the time of an anaphylactic reaction, the anaesthetist can retrieve the necessary instructions and forms from the website of the Norwegian association of anaesthetists ('Anaphylaxis kit', www.nafweb.no). Basic patient data and clinical details of the adverse event are documented, and acute in vitro diagnosing and reporting to authorities are ensured. Customized laboratory requisitions aid analysing serum samples drawn within 2 h and after 24 h from start of reaction, respectively, and, if available, samples taken before the reaction.

Sera and forms are sent to the Laboratory of Clinical Biochemistry, Haukeland University Hospital in Bergen, Norway.

Serum tryptase and IgE antibodies to pholcodine and suxamethonium are analysed using the ImmunoCap® system. Surplus sera are stored at -80°C. Based on the acute laboratory test results and the case history, a preliminary diagnostic suggestion is made as to severity grade, suspected causative agent and the reaction mechanism. Reported cases not related to general anaesthesia, reactions occurring >24 h after induction of anaesthesia or reports not containing the required information are excluded.

Table 27 summarises the 650 acute cases reported to the NARA database from 2005 to 2013. The results show a reduction in total reports across the 9-year period, but the percentage of reports due to an NMBA remains approximately stable.

Table 28 shows that when grouped into 3-year blocks, the percentage of cases due to an NMBA with positive IgE to suxamethonium and pholcodine decreases from 15.7% to 5.7% and 35.9% to 24.6%, respectively.

Official sales data for NMBAs in Norway across the three time periods is shown in Table 29 for reference.

Comments:

The number of reports of anaphylaxis to NARA trended downwards from 2005 to 2013. The trend is better reflected in the aggregated data for the three-year blocks, which shows 270 reports for 2005-2007 (P0), 205 reports for 2008-2010 (P1), and 175 reports for 2011-2013 (P2). The proportion of reports in which an NMBA was used also declined slightly over this period from 72.2% (P0) to 67.4% (P2).

Not surprisingly following withdrawal of pholcodine, the proportion of NMBA-anaphylaxis cases that had IgE antibodies to pholcodine declined significantly from 35.9% (P0) to 24.6% (P2) over this period (presumably because the removal of pholcodine from the market meant that there was little change of pholcodine boosting IgE levels).

The proportion of patients who had IgE antibodies to suxamethonium (which represents the QAI) also declined, from 15.9% (P0) to 5.7% (P2). This reduction in sensitisation to QAI indicates that fewer patients who had anaphylaxis during anaesthesia in fact reacted to the NMBA. However, the study does not report on other possible causes for the anaphylactic reaction (eg, antibiotics, latex).

As noted previously, the NARA database is likely to be subject to similar reporting biases as for other spontaneous adverse reaction reporting programs. There may have been some drop-off over time in reporting of anaesthetic anaphylaxis, particularly after the drug held to be responsible was removed from the market.

This data supports the pholcodine hypothesis in that the proportion of NMBA-anaphylactic cases that were in fact due to the NMBA dropped following withdrawal of pholcodine from the market in Norway.

3.4 Company reports

Medsafe requested the sponsors of pholcodine-containing products to request to provide efficacy, safety and usage information for each of their products[3]. Medsafe has received responses from iNova and Johnson & Johnson. Their responses are summarised below.

3.4.1 iNova

[3] On 5 September 2019,

[redacted]

3.4.2 Johnson & Johnson

[redacted]

4 DISCUSSION AND CONCLUSIONS

NMBA-induced anaphylaxis

Anaphylaxis during anaesthesia is a relatively rare occurrence, but when it does occur it is immediately life-threatening and, in some cases, fatal.

NMBAs account for the majority of cases of anaesthetic anaphylaxis, followed by antibiotics and latex. Among the NMBAs, suxamethonium appears to have the highest rate of anaphylaxis (11.1 per 100,000) [31].

More than half of patients who experience anaphylaxis to an NMBA have not previously been exposed to the medicine, or indeed to any NMBA [33]. Prior sensitisation is an essential component of IgE-mediated anaphylaxis, so a molecule with the same allergenic epitope – the QAI – must be responsible for the sensitisation.

Rates of NMBA-induced anaphylaxis vary by country. Of particular note was the observation that rocuronium-induced anaphylaxis was six times higher in Norway than in neighbouring Sweden [22].

In 2005, Florvaag and colleagues undertook a study to document the prevalence of IgE sensitisation to NMBAs in Norway and Sweden, and explored whether various household and environmental chemicals may have caused sensitisation. The study compared IgE antibodies to suxamethonium and morphine in sera from blood donors and patients with suspected allergy from both countries, and from Norwegian patients who had experienced anaphylaxis to a NMBA. In Norway 0.4% of blood donors, 3.7% of 'Allergics' and 38.5% of 'Anaphylactics' were IgE-sensitized to suxamethonium, and 5.0%, 10.0% and 66.7%, respectively, to morphine. None of the sera from Sweden were positive. The majority (69%) of those sensitised were women. Several household chemicals exhibited suxamethonium and/or morphine activity, but the only difference between Norway and Sweden was cough mixtures containing pholcodine. IgE antibodies to pholcodine were found to

be present in 6.0% of blood donors from Norway but in no serum from Sweden. This finding initiated the 'pholcodine hypothesis'. [32]

In 2007, the same research group found that serum levels of IgE antibodies to morphine, pholcodine and suxamethonium increased significantly in patients with a history of NMBA-induced anaphylaxis after exposure to cough syrup containing pholcodine. [35]

In 2009, the same authors recalled that pholcodine had been marketed in Sweden during the 1970s and 1980s. Using stored serum samples from 1970-1999, they compared IgE antibodies to morphine, pholcodine and suxamethonium. The percentage of sera with antibodies to pholcodine and morphine dropped from the 1970s to the 1990s, although the pattern was less clear with suxamethonium. [36]

In 2010, a multicentre study compared the percentage of serum samples from atopic individuals that were IgE-sensitised to pholcodine, morphine and suxamethonium in low and high pholcodine-consumption countries. The study found that low consumption countries (Denmark, Finland, Germany and Sweden) generally had very low percentages (<1%) of samples that were sensitised to pholcodine, morphine or suxamethonium, while high consumption countries (France, Norway and the UK) had higher percentages (2.4-7.0%). However, there were some discrepancies. The United States, where pholcodine has never been marketed, 2% of samples were positive for IgE antibodies to pholcodine. The Netherlands also had and unexpectedly high percentage (4.9%), but despite no marketed drugs, there was still moderate consumption of pholcodine in the country. [37]

Following withdrawal of pholcodine from the Norwegian market in March 2007, the prevalence of IgE sensitisation to pholcodine, morphine and suxamethonium in serum samples obtained from the allergy diagnostic laboratory in Bergen dropped significantly at 1 year, 2 years and 3 years. The proportion of NMBA cases reported to NARA with positive antibodies to suxamethonium (implicating the NMBA) also declined. [38]

A French study in 2013 demonstrated a 4.6-fold higher frequency of positive IgE against QAIs in hairdresser apprentices, compared with other apprentices, suggesting that exposure to other environmental QAIs may contribute to NMBA sensitisation. [41]

In 2014, a study similar to the multicentre study undertaken by Johansson in 2011, showed that in Australia where pholcodine is readily available, a higher proportion of serum samples (from allergy clinic attendees) had antibodies to suxamethonium and pholcodine compared to very few in Japan and the Republic of Korea where pholcodine is not available. However, despite the medicine not being available in Japan and Korea, approximately 1% of samples from each country had antibodies to pholcodine. [42]

In 2013, six years after pholcodine was withdrawn from the Norwegian market, reports to the NARA database had continued to decline (possibly suggesting reporter-fatigue), but the proportion of cases that tested positive for IgE-suxamethonium (implicating the NMBA as the causal agent) also declined significantly [43]. Information on IgE antibodies to other potential allergens such as antibiotics and latex was not reported.

These studies, most of which were undertaken by a single research group, show an ecological association between pholcodine and NMBA-induced anaphylaxis. However, none of the studies provide direct evidence of a causal association.

The EMA reviewed the evidence for a link between pholcodine and NMBA-induced anaphylaxis in 2011. They considered the evidence available at the time to be circumstantial, not entirely consistent, and insufficient to support the conclusion that there is a significant risk of cross-sensitisation to NMBAs. Key issues raised by the EMA were:

- Most of the data came from a single research group and comprised ecological studies
- Other factors may explain the observations. Eg, NARA had been less intensely promoted in latter years, so the observed decrease in reporting may have reflected a lower reporting rate rather than lower occurrence of NMDA-associated anaphylaxis.
- The absence of any report of IgE-mediated anaphylactic reaction to NMBAs in Sweden since 1990 raised questions on the reliability of the data, as regardless of pholcodine use, NMBAs would still be

expected to cause anaphylactic reactions, and the Swedish data did not reflect the expected background rate.
- Changes in anaesthetic procedures, type of products used in anaesthesia, and overall use of NMBAs could play a role in explaining the findings.
- Assuming biological plausibility, a broad range of other substances containing the same QAI structure could also potentially induce cross-sensitisation to NMBAs.
- Data from the US and the Netherlands did not neatly fit the hypothesis as, although pholcodine was not marketed in these countries, prevalence of IgE to pholcodine and morphine was found to be high.
- Anaphylaxis to pholcodine itself appear to be rare.

However, the EMA did consider that the possibility of association warranted further investigation and required Market Authorization Holders to submit a protocol for a case-control study. No information was found to indicate that such a study has since been completed.

It should be noted that the EMA's review was undertaken before either the Australia/Japan/Korea study or the review of cases in the NARA database 6 years after pholcodine was withdrawn from Norway.

The Australian and New Zealand College of Anaesthetists together with the Australia and New Zealand Anaesthetic Allergy Group have expressed concern to Medsafe about the ongoing easy availability of pholcodine, and submitted an objection to the MCC's decision to maintain its current pharmacy-only classification (see Annex).

Other safety issues

The information available on the safety of pholcodine use in the context of acute cough is limited. There are no adequate clinical trials for either short-term or long-term safety. Reports received by CARM for products that clearly contain pholcodine mainly concern allergic reactions (including anaphylaxis), [redacted]

Efficacy

Pholcodine has been used in New Zealand since the 1960s. It is a 'grand-fathered medicine and as such its efficacy has not been subjected to the same scrutiny as medicines that are approved today. The available clinical data is limited. Most of the studies were small, had poor patient selection, were not adequately controlled with either active or placebo, and in some studies pholcodine was used in combination products so that it was not possible to attribute any observed effect solely to pholcodine. The most recent study [14] compares pholcodine and dextromethorphan in patients with acute cough. The study aimed to assess the non-inferiority of pholcodine. Both medicines had similar effect on cough, but pholcodine had fewer treatment-emergent adverse events. However, the study did not include a placebo arm, so any observed improvement in cough is difficult to distinguish from the expected natural recovery from the underlying acute viral illness.

Benefit-risk balance

Pholcodine is an old medicine with assumed efficacy. The available clinical trial data neither supports nor refutes the efficacy of this medicine. [redacted] These medicines are not funded, so there must be some perceived benefit among consumers.

However, acute cough due to upper respiratory infection is a self-limiting condition that is usually not associated with any serious consequences.

The unproven, widely perceived benefits of pholcodine for self-limiting, acute, non-productive cough must be weighed against the ecological evidence suggesting that pholcodine may be associated with an increased risk of life-threatening, and in some cases fatal, anaphylaxis in a small number of patients exposed to NMBAs during anaesthesia.

5 ADVICE SOUGHT

The Committee is asked to advise:

- on the evidence of efficacy
- on the evidence for safety
- the strength of the evidence that pholcodine predisposes patients to anaphylaxis with NMDAs (all or a subset)
- whether the balance of benefits and risk for the use of pholcodine for the symptomatic treatment of non-productive cough is favourable
- any regulatory action is required to improve the balance of benefits and risks

6 ANNEXES

1. ANZAAG and ANZCA objection to MCC61 decision re pholcodine [Confidential]
2. iNova. Pholcodine Safety and Efficacy Overview [Confidential]
3. Johnson and Johnson. Rationale supporting the revision of the 2019 CCDS for oral non-prescription pholcodine products [Confidential]
4. EMA_2012_Assessment report for Pholcodine containing medicinal products
5. Florvaag, Johansson, et al, 2005
6. Johansson, Florvaag, et al, 2010
7. Florvaag, Johansson, et al, 2011
8. Dong, Acouetey, et al, 2013
9. Katelaris, Kurosawa, et al, 2014
10. De Pater, Florvaag, et al, 2017

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