

WHAT SHOULD COUGH MIXTURES CONTAIN?

A/Prof Cheong Pak Yeap

INTRODUCTION

'Cough mixtures' are commonly prescribed by family physicians (FPs) and purchased over-the-counter by patients for self-medication. These mixtures commonly contain multiple drugs in various formulations. FPs should therefore know exactly what drugs these mixtures contain and how each drug works. This article examines traditional concepts regarding cough mixtures and proposes a rational approach based on patho-physiology when prescribing these mixtures.

TRADITIONAL CONCEPTS

Suppressants and expectorants

It is traditionally taught that cough mixtures could be classified as either suppressants or expectorants, with the former containing drugs that suppress the cough centres in the brain and yet others as expectorants or mucolytics, because they are supposed to increase bronchial secretion and actively expel phlegm. Traditional authorities such as Martindale Pharmacopoeia¹ support this notion by classifying cough medicine into "Cough Suppressants, Expectorants and Mucolytics". We can therefore understand why an inadequate algorithm of 'suppress or expel' is often used by many family physicians when prescribing cough mixtures.

Pro-tussives And Anti-tussives

Irwin and Curley from the Division of Pulmonary and Critical Care Medicine, University of

Massachusetts, reviewed the subject in various papers and concluded that drugs that make cough more effective ("pro-tussive") are of no practical significance. In clinical practice, cough medicine that work as 'anti-tussive' can be defined as therapy that controls, prevents and eliminates cough. In their paper 'Appropriate use of anti-tussive and pro-tussive – a practical review'², they emphasised that the 'efficacy of pro-tussive therapy has not been well documented. Therapies such as hypertonic saline aerosol and erdosteine in patients with bronchitis, and amiloride aerosol in patients with cystic fibrosis have been shown to improve mucus clearance but the clinical utility has not been adequately studied'.

This view was also shared by Fuller and Jackson (1990)³. In an editorial on the subject in *Thorax*, these authors reiterated 'the treatment of productive cough will depend on the manipulation of mucus secretions which so far does not appear to be possible in man'. Hence, the pro-tussive idea is theoretical.

'Expectorant' cough mixtures traditionally contain drugs like ammonium chloride are supposed to act by increasing mucus production and aid in expectoration (i.e. pro-tussive). These notions are extrapolated from animal studies. For example, ammonium chloride does stimulate both gastric and bronchial secretions in large doses in animal models. However, to achieve the increased bronchial secretion in humans, large and gastric ulcer inducing doses have to be administered. In the lower dosages found in cough mixtures, these drugs actually work by altering mucociliary action on the cough receptors – an anti-tussive and not a pro-tussive action.

The conclusion from papers in the literature then is that in practice, there is anti-tussive action

CHEONG PAK YEAN, MBBS, MMed(Int Med), MRCP(UK),
FCFP, FAMS, FRCPE

Adjunct Associate Professor, Department of Community Occupational
and Family Medicine, National University of Singapore

but not pro-tussive action that may be obtained from therapeutic agents acting on the symptom of cough.

Understanding the term “expectorants”

For better understanding, it is therefore best not to use the term “expectorants” or else to consider both expectorants and mucolytics as one functional group with anti-tussive action (through their action on altering the muco-ciliary factors on cough receptors). This is the opinion not only of authorities like Irwin and Curley, but also clinicians such as Professor Murtagh⁴ when deciding what components in cough mixture should be prescribed in practice. We can now try to construct a rational approach to the symptom of cough.

A RATIONAL APPROACH

Concept of Definitive Anti-Tussive Therapy and Non-definitive Anti-Tussive Therapy

In another review paper (‘The treatment of cough—a comprehensive review’ published in *Chest* June 1991)⁵, Irwin and Curley proposed a rational approach by considering both the cause of the cough and also the cough reflex when instituting therapy. Taken this way, cough mixtures can be regarded as medications for definitive anti-tussive therapy or non-definitive anti-tussive therapy.

Definitive anti-tussive therapy. Definitive anti-tussive therapy to eliminate cough comprise of measures directed in a specific way against the aetiology (eg. Killing the tubercle bacilli) and/or the presumed operant patho-physiologic mechanism responsible for the cough (eg, eliminating the postnasal drip in allergic rhinitis). These are shown in Table 1.

Non-definitive Anti-tussive Therapy. Non-definitive anti-tussive therapeutic agents comprise of medications that work on the various sites of the cough reflex to block the completion of the reflex as shown in Table 2. A knowledge of the sites of cough reflex arc and actions of medications on these sites to cut off the cough will be useful in practice.

Concept Of Classifying Cough Mixtures By Pharmacological Group

Cough medicine work by affecting one or more of the above mechanisms. For example, diphenhydramine used to treat the common cold acts centrally on the cough centre to counter the irritation from the postnasal drip, as well as an anti-histamine to reduce excessive secretions in the nose.

It is therefore more useful to classify common cough mixtures by its pharmacological content. Common cough medicine belong to five pharmacological groups namely:

1. Antihistamines such as brompheniramine;
2. Sympatho-mimetic drugs such as pseudoephedrine as decongestant;
3. Mucolytic/Expectorants as one functional group;
4. Cough Centre suppressants in the brain-stem; and
5. Demulcents

Clarifying Misconceptions

Misconceptions often exist regarding mucolytic and expectorants and these should be clarified. They are summarised and elaborated in Table 3.

Table 1: Definitive Anti-tussive Therapy

Clinical Diagnoses	Therapeutic Agents for Definitive Therapy
Bronchial Asthma	steroids, bronchodilators
Postnasal Drip Syndrome (PNDS)	Decongestant nose spray, Antihistamines, sympatho-mimetic medicine (so-called decongestant).
Sinusitis	PNDS plus antibiotics
Cardiac failure	digoxin, furosemide
gastro-esophageal reflux (GERD)	H2-antagonist
ACE-inhibitors side-effect	substituting other anti-hypertensive therapy

Table 2: Non-definitive Anti-tussive Therapy

Site of cough reflex arc altered	Therapeutic agents and desired actions	Remarks
Alter muco-ciliary factors irritating cough receptors	<p>"Mucolytics" purportedly</p> <ul style="list-style-type: none"> o decrease the production of mucus o change the consistency or regulation of mucus eg. mucolytics o increase muco-ciliary clearance and hydration on lower respiratory 	<p>Conflicting results of efficacy were found in mucolytics such as bromhexine and S-carboxymethylcysteine.</p> <p>The effects of ammonium chloride tract secretions are not yet adequately evaluated</p>
Increase the threshold or latency of afferent limb i.e. cough receptors itself or the afferent nervous pathway	<p>Local anaesthetic and demulcents.</p> <ul style="list-style-type: none"> o The effect of local anaesthetic is self-explanatory o Demulcents act to decrease the stimulation of cough centres in the bronchial tree or by flooding the cough centres with sub-maximal impulses 	<p>Throat lozenges commonly contain local anaesthetic. Examples of demulcents are the sugar and menthol found in cough mixtures.</p>
Increase the threshold or latency of cough centre in the brain-stem i.e. cough centre suppressant	<p>Narcotic and non-narcotic cough suppressants</p> <ul style="list-style-type: none"> o The desired effect is direct cough suppression 	<p>Diphenhydramine commonly considered an 'expectorant' is actually a non-narcotic cough suppressant. This has been demonstrated in a study on its anti-tussive effect on the cough of chronic bronchitis of having an effect independent of its anti-histamine action.⁶</p>
Increase the threshold and latency of the efferent limb	Aerosolized Ipratropium bromide	Used in treatment of cough of Chronic obstructive airway disease
Decrease strength and contraction of the respiratory skeletal muscle	Narcotics and neuromuscular blocking agents to suppress cough artificially ventilated patients	Not used in family practice setting

Table 3 : Common misconceptions on cough mixtures

1.	Though drugs used for non-specific treatment of cough could theoretically either prevent, control or eliminate cough (anti-tussive) when the cough is non-productive or to facilitate cough when it is productive (pro-tussive), drugs with pro-tussive actions are not available for clinical use. Therefore, the simple algorithm classifying cough mixtures into suppressants for 'dry' cough and expectorant for 'wet' cough is inappropriate.
2.	There is a common misperception that expectorants act as pro-tussives. There is no evidence of that action in humans. Irwin and Curley, two distinguished authorities on this subject, classified expectorants as anti-tussive that act by altering muco-ciliary factors on the cough receptors.
3.	There should therefore be no objections to the use of cough centre suppressant in combination with medicine acting, by altering muco-ciliary factors on cough receptors. Their actions are synergistic and not antagonistic.
4.	Mucolytics and expectorants should also be functionally considered as one functional group which work by their anti-tussive action on the cough receptors. A clinical approach to the treatment of cough should include identifying specific and non-specific causes and how each of the five groups of drugs commonly found in cough mixtures.

Mucolytics. There is no universal agreement on the place of mucolytic in treating cough. Studies have shown that mucolytics do not objectively decrease the number of cough counts (nor increase them). Subjective benefits of guaifensin⁷ often classified as a mucolytic has however been demonstrated. A paper by Kuhn JJ et al on the anti-tussive effect of guaifensin in young adults with natural colds demonstrated no objective anti-tussive effect compared to placebo, but the subjects with productive cough receiving the medicine reported a decrease in sputum thickness and quantity.

Expectorants. Diphendramine Hydrochloride is often wrongly thought of as an expectorant

drug, whereas it is actually an anti-histamine with independent non-narcotic cough centre suppressant action. It does not act on the muco-ciliary factors and is neither an expectorant nor a mucolytic. This fact should be reflected in pharmacopeias that are commonly used, as for example, the Standard Drugs Formulary 1998⁸ of the Ministry of Health Singapore.

Combination. There is also a common misconception that mucolytics and expectorants as functional groups should not be combined with central cough centre suppressants such as phocodeine, even though their actions are synergistic on different sites of the cough reflex and not antagonistic.

CONCLUSION

The new approach to treating cough should be to consider firstly, definitive measures against the aetiology and secondly, non-specific measures against the cough reflex. Then, common drugs from the five pharmacological groups that would be useful to treat the cough should be identified. The cough mixture with appropriate dosage of these drugs so identified could then be prescribed.

REFERENCES

1. Martindale. Cough Suppressants Expectorants and Mucolytics 741.
2. Irwin RS, Curley FJ, Benett FM. Appropriate use of anti-tussive and protussive – a practical review *Drugs* 1993 Jul; 46(1): 80-91.
3. Fuller, Jackson Physiology and treatment of cough Editorial *Thorax* 1990; 45: 425-30.
4. Murtagh Problem-Solving in General Practice 384 In *Textbook of Family Medicine* 1998.
5. Irwin RS, Curley FJ. The treatment of cough – a comprehensive review *Chest* 1991 99: 1477-84.
6. Lilienfield LS, Rose Jc, Princiotta JV. Antitussive activity of Diphendramine in Chronic cough *Clin Pharmacol Ther* 1976 Apr; 19(4): 421-5.
7. Kuhn JJ et al. Antitussive effects of guaifenesin in young adults with natural colds-objective and subjective assessment. *Chest* 1982 Dec; 82(6): 713-8.
8. Ministry of Health Formulary 1998 Standard Drugs Ministry of Health 153.