Common Cold
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Over the counter medicines for colds

Ronald Eccles

Common Cold Centre, Cardiff School of Biosciences, Cardiff University, Museum Avenue, Cardiff CF10 3AX, UK

Abstract

Over the counter (OTC) medicines may be defined as medicines that are freely available to the public without a prescription from a doctor. Self-medication for common cold is now encouraged by most government health authorities in order not to overload health resources in winter. This chapter examines the efficacy of the different groups of medicines for the relief of common cold symptoms (analgesics, decongestants, antihistamines, antitussives, menthol, expectorants and mucolytics, throat lozenges and sprays, multi-symptom products, and hot drinks). Safety is the most important factor in any common cold medicine because of the widespread use of the medicines. Because of limitations in dose due to safety concerns many OTC medicines are used at the limits of efficacy and there is often little clinical data to support efficacy, and safety is often supported from a long history of safe use. Aspirin, paracetamol and ibuprofen are the most widely used analgesic treatments to alleviate pain and fever both as monotherapies and in combination with other cold medicines and their efficacy and safety is supported by data from trials on other pain models. The efficacy of nasal decongestants can be supported by clinical trials, and similarly the symptom relief provided by menthol for nasal congestion. The efficacy data for antihistamines, and antitussives is limited and controversial, and there is no real clinical support for the efficacy of expectorants and mucolytics. There is no doubt that all of the OTC common cold medicines are popular with consumers and that they do provide relief from symptoms that in some cases may be more due to a placebo effect than a pharmacological effect of an active ingredient. Multi-symptom medicines provide a safe and convenient way of treating the common cold syndrome of multiple symptoms but their use is sometimes criticised when not all symptoms need to be treated. Hot drinks can provide immediate and sustained relief from symptoms, especially cough and sore throat.

Introduction

Over the counter (OTC) medicines may be defined as medicines that are freely available to the public without a prescription from a doctor. The term OTC is widely used in Europe and the USA, although it is a little confusing, as most medicines are freely available on the pharmacist or supermarket

shelf and only certain medicines are kept out of reach at the pharmacist. The OTC common cold market presents a huge business opportunity to the pharmaceutical companies, but there is relatively little research undertaken by the pharmaceutical industry in the development of new medicines for this condition. OTC common cold medicines, with few exceptions, are marketed for the relief of common cold symptoms, and they do not prevent or alter the viral cause of a common cold. Since most colds are acute self-limiting conditions the goal of controlling symptoms is a reasonable goal for OTC medicines, as symptom relief will allow the patient to carry on with their life.

In recent years there has been an increased focus on safety issues associated with OTC common cold medicines. Antitussives such as codeine have always been at risk of increased regulatory control or a ban due to the potential risk of abuse [1] and recently the recreational abuse of dextromethorphan has led to restrictions on sale or a ban in many countries [2, 3]. Nasal decongestants because of their vasoconstrictor activity have the potential to cause cardiovascular side effects and safety concerns led to a ban on the sale of phenylpropanolamine in the USA in 2000. More recently, concerns over the recreational abuse of the nasal decongestant pseudoephedrine have led to the loss of its OTC status in many countries and its substitution in many products with a relatively less-well-characterised decongestant, phenylephrine [4].

The loss or restriction of many popular cold medicines in recent years due to safety issues means there are fewer active ingredients available to the pharmaceutical industry. Each company has access to the same limited pool of active ingredients, and the marketing of these active ingredients is mainly on the brand name or on claims about strength or speed of action. Because of the focus on advertising rather than research, the pharmacology of the OTC common cold active ingredients has been neglected as a review topic in scientific and medical journals, and it is hoped that this chapter will be of use to those doctors, pharmacists and brand managers who need an overall review of the active ingredients commonly used in cold treatments.

This chapter discusses the active ingredients that make up many of the OTC medicines. The OTC medicines are divided into several groups for discussion: analgesics, decongestants, antihistamines, antitussives, expectorants and mucolytics, menthol and other aromatics, sore throat lozenges and sprays.

Analgesics

Analgesics such as aspirin, paracetamol (acetaminophen in the USA) and ibuprofen are the most common treatments for common cold, either as mono-medicines or in combination with other cold medicines such as anti-

histamines and nasal decongestants. The use of analgesics as treatments for colds and flu has recently been reviewed [5].

Medicines

The analgesics, aspirin, paracetamol and ibuprofen can provide relief for a range of common cold symptoms such as headache, sore throat pain, fever, muscle aches and pains, sinus pain, and earache [5].

Analgesics are usually marketed as combination medicines for treatment of common cold, and these medicines may be formulated as tablets, capsules, hot drinks, effervescent drinks and syrups. Analgesics are often combined with a nasal decongestant or an antihistamine, and in some multi-symptom products the analgesic may be combined with nasal decongestant, antihistamine and antitussive or expectorant.

Pharmacology

Aspirin and ibuprofen are usually classified as non-steroidal anti-inflammatory drugs (NSAIDs) as they have anti-inflammatory actions in high doses, whereas paracetamol (acetaminophen) is not usually classed as an NSAID as it does not have any anti-inflammatory activity. The three analgesics have a similar mode of action in treating the pain and fever symptoms of common cold as they all inhibit the activity of cyclooxygenase (COX) enzymes responsible for the biosynthesis of prostaglandins and related inflammatory mediators [6]. Prostaglandins play an important role in the inflammatory response to infection as they cause local vasodilation and nasal congestion, and also potentiate the local pain effects of bradykinin, to cause sore throat pain, earache and sinus pain [7]. The sensitisation of pain nerve endings in the upper airway by prostaglandins leads to the pain symptoms of common cold and the inhibition of prostaglandin synthesis by the analgesics provides relief from local pain symptoms such as sore throat pain [8, 9].

The generation of common cold symptoms can be divided into two components: a local response to cellular damage that causes the local synthesis of inflammatory mediators such as bradykinin and prostaglandins; and a systemic response caused by cytokines released from macrophages and neutrophil granulocytes [7, 10]. The cytokines circulate in the blood stream to the brain to cause headache and fever and they also initiate muscle aches and pains. These systemic responses are mediated by prostaglandin synthesis [11] and the inhibition of prostaglandin synthesis by the analgesic will therefore relieve the common cold symptoms of headache, fever and muscle aches and pains as well as localised pain symptoms in the upper airway.

Paracetamol is believed to act as an analgesic and antipyretic by inhibiting prostaglandin synthesis in the pain pathways in the central nervous

system, whereas aspirin and ibuprofen act to inhibit prostaglandin synthesis both in the brain and in peripheral tissues. It is the peripheral action of aspirin and ibuprofen on prostaglandin synthesis that is responsible for any anti-inflammatory effects.

Efficacy

Considering the widespread use of analgesics in treating common cold symptoms, it is surprising that there is relatively little literature on the efficacy of analgesics in colds, and that most of the efficacy and safety data must be derived from studies on other pain and fever models [5].

Placebo-controlled studies have demonstrated the efficacy of aspirin as a treatment for sore throat pain, fever and muscle aches and pains associated with common cold [9, 12–14]. The effects of a single dose of 800 mg aspirin on sore throat pain associated with common cold are illustrated in Figure 1. The graph shows the differences in pain intensity compared to a baseline score before treatment and the relatively large placebo response is typical

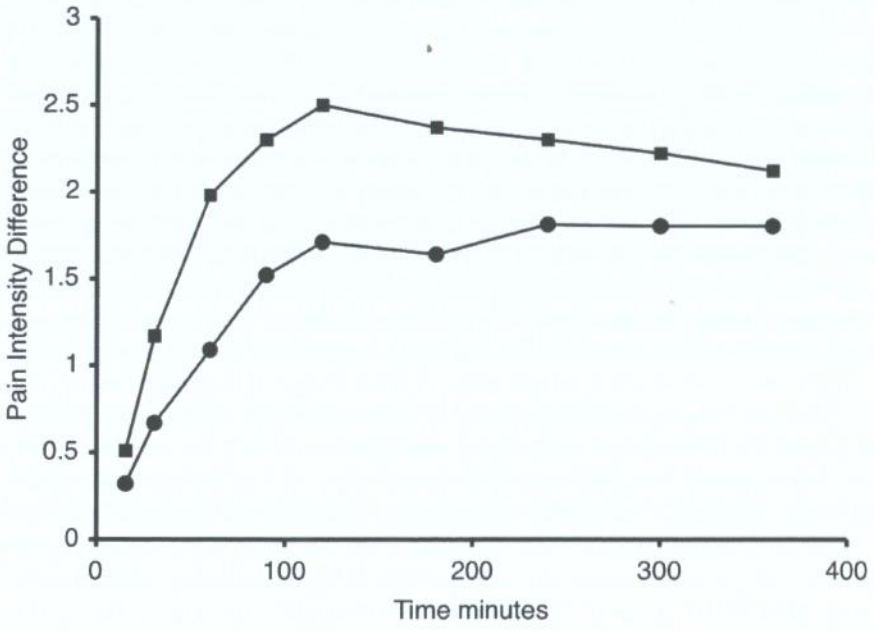

Figure 1. Effects of a single dose of 800 mg aspirin on scores for pain intensity in patients with sore throat pain associated with common cold. The scores represent the mean differences in pain intensity from the baseline scores. Square symbols represent scores for the aspirin treatment group and round symbols for the placebo treatment group. The graph is based on the results of a published clinical trial on the efficacy of aspirin [9].

of most pain studies. Similarly, paracetamol has been shown to be an effective analgesic for pain and fever symptoms associated with common cold [12, 14–16]. Ibuprofen is the most recent analgesic to achieve OTC status for treatment of common cold and, although the efficacy of ibuprofen has been established in various pain and fever models, there is very little information available on its efficacy as a treatment for colds. Clinical trials have shown ibuprofen to be an effective treatment for sore throat pain, headache, fever, earache, sneezing and muscle aches and pains [15, 17].

Although it is generally accepted that aspirin and ibuprofen have anti-inflammatory actions when used in the treatment of rheumatoid arthritis, there is no convincing evidence that they have anti-inflammatory effects in common cold treatment when used in the normal OTC dose range [5]. No convincing case can be made for a difference in efficacy between aspirin, paracetamol and ibuprofen for treatment of pain and fever associated with common cold [5]. However, a combination of paracetamol plus ibuprofen may be superior on some parameters to either drug alone in treatment of fever-associated discomfort in children aged between 6 months and 6 years [18].

Safety

In considering the safety of the analgesics for treatment of symptoms of upper respiratory tract infection (URTI), it is necessary to understand that much of the concern over the use of NSAIDs such as aspirin and ibuprofen is related to long-term therapy with higher doses than available for OTC use, for example in the treatment of chronic rheumatoid arthritis. Similarly, concerns about the safety of paracetamol are often linked to alcohol abuse and overdose. Because of the limited number of trials on the use of analgesics in patients with URTI, it is necessary to rely on safety data gathered from trials on indications other than URTI.

The major concerns about safety are related to liver damage with paracetamol, especially in overdose, and in relation to alcohol ingestion. Aspirin may cause gastric irritation, bleeding and exacerbation of asthma. Ibuprofen may also cause gastric irritation and bleeding. However, all three analgesics are generally recognised as having a good safety profile when used in OTC doses for the treatment of acute pain and fever associated with common cold [5]. There is little evidence for any difference in overall safety between the analgesics, although special cases can be made for contra-indications such as for aspirin in children (Reye's syndrome), and for paracetamol in cases of excess alcohol intake.

The discovery of two different enzymes for prostaglandin synthesis, COX-1 and COX-2, has revolutionised the development of new analgesic anti-inflammatory drugs. COX-1 is the constitutive enzyme found normally in tissues such as the stomach and kidney and inhibition of this enzyme

system is responsible for side effects such as gastric irritation. COX-2 is the enzyme that is induced by inflammation and there is interest in developing specific COX-2 inhibitors in order to have a more specific analgesic and anti-inflammatory effect [19, 20]. The development of specific COX-2 inhibitors may eventually provide new analgesics that will gain OTC status in the future for treatment of common cold but at present this is a distant goal and much more information is needed on the side effect profiles of COX-2 inhibitors before they could become freely available without prescription.

Effects on the immune system

High doses of NSAIDs such as ibuprofen and aspirin have a depressant action on the immune response and this is beneficial in diseases such as rheumatoid arthritis where the autoimmune response causes damage to joints. However, a depressant action on the immune system would not be beneficial in the treatment of URTI, and analgesics are sometimes implicated in prolonging the course of infections, especially when the infection is associated with fever [21]. There is no evidence that treatment with analgesics interferes with the natural recovery from URTI but there are reports that aspirin and paracetamol may increase the severity of the symptom of nasal obstruction associated with URTI. A single dose of 900 mg aspirin has been reported to cause an increase in nasal resistance to airflow in healthy volunteers [22] and there is one report that daily doses of 4000 mg aspirin and paracetamol caused nasal congestion when used by volunteers infected *via* rhinovirus challenge [23].

Conclusions

Aspirin, paracetamol and ibuprofen are the most commonly used analgesic treatments for common cold in both adults and children. In OTC doses they are safe and effective, and apart from their specific contraindications, there is little difference between the analgesics as regards safety and efficacy.

Nasal decongestants

The nasal decongestants fall into three groups: topical nasal decongestants administered as a nasal spray or nose drops (oxymetazoline, xylometazoline and phenylephrine); oral decongestants that may be formulated as a tablet or syrup (ephedrine, pseudoephedrine and phenylephrine); and inhaler sticks containing ephedrine (also known as levo-methamphetamine or leveometamfetamine in the USA).

Medicines

The oral decongestants pseudopehedrine and phenylephrine are usually formulated as a combination medicine with an analgesic in tablet formulations, and they may also be combined in multi-symptom treatments with antihistamines and antitussives. The topical nasal decongestants are usually formulated as a mono-therapy nasal spray that may also contain menthol and other aromatics. More recently there has been interest in developing a combination treatment for congestion and runny nose by combining xylometazoline with ipratropium [24].

Pharmacology

The nasal decongestants open up the nose by constricting the large nasal veins in the anterior part of the nose that control nasal airway resistance [25]. The medicines are sympathomimetics in that they mimic the effects of the sympathetic neurotransmitter noradrenaline or facilitate its release from sympathetic nerve endings [26]. Both the topical and oral decongestants achieve nasal decongestion by acting on alpha receptors on nasal veins to cause constriction of vascular smooth muscle [25].

Efficacy

The topical decongestants oxymetazoline and xylometazoline have a rapid onset of action, as they are applied directly to the nasal epithelium and quickly reach the nasal blood vessels to cause vasoconstriction. Decongestion is achieved within 5–10 minutes and sustained for up to 10 hours as shown in Figure 2. The oral decongestants pseudophedrine and phenylephrine have a slow onset of action over 30–60 minutes, as they must first be absorbed from the gut to achieve their action on nasal blood vessels. The efficacy of topical and oral decongestants is compared in Figure 3, which demonstrates that the oral decongestants improve nasal conductance by around 10% compared to a 70% change in nasal conductance associated with topical decongestants. The efficacy of the topical nasal decongestants oxymetazoline and xylometazoline is not in doubt, as large changes in nasal conductance can be easily shown in clinical trials [25, 27], but the efficacy of the oral decongestants pseudoephedrine and phenylephrine is more difficult to show in clinical trials. Published clinical trials on pseudoephedrine have reported significant but small changes in nasal airflow measured by rhinomanometry [16, 28], but there are no good quality published studies on the efficacy of phenylephrine as an oral decongestant, and its efficacy may be limited by first pass metabolism of phenylephrine in the gut [4]. Meta-analysis of studies on phenylephrine

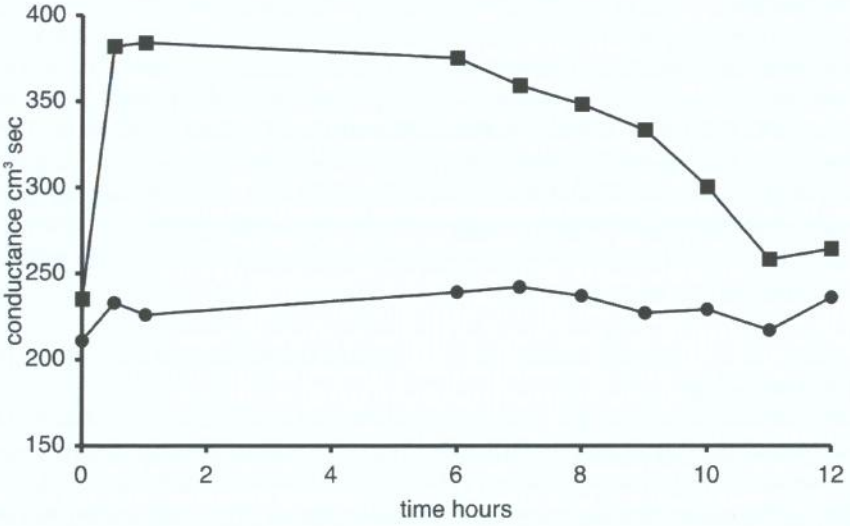

Figure 2. Effects of a single spray of 0.1% xylometazoline topical nasal decongestant on nasal airflow measured by rhinomanometry in patients with nasal congestion associated with common cold. The placebo treatment was a saline nasal spray. Square symbols represent airflow for the xylometazoline treatment group and round symbols for the placebo treatment group. The graph is based on the results of a published clinical trial on the efficacy of xylometazoline as a nasal decongestant [27].

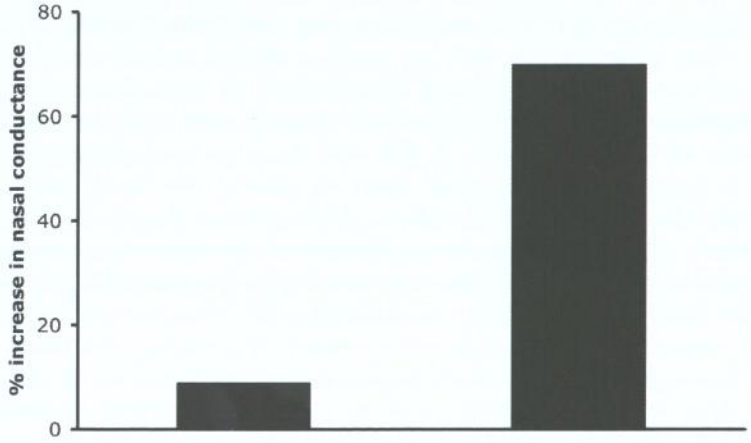

Figure 3. Effects of oral and topical decongestants on nasal airflow. The figure shows the percentage increase in nasal conductance as measured by rhinomanometry for a single oral dose of 60 mg pseudoephedrine or one spray in each nostril of 0.1% xylometazoline, in patients with nasal congestion associated with common cold. The change in conductance was measured at 60 minutes after treatment and is expressed as a mean percentage change relative to the change in conductance observed in the placebo treatment group. The results are calculated from the data reported in clinical trials [27, 28].

held on file by the FDA have provided divergent views on efficacy [29, 30].

Ephedrine is used in wick inhalers to treat nasal congestion but no references have been found to support the efficacy of inhaled ephedrine as a nasal decongestant.

Safety

Safety issues are mainly related to cardiovascular events as the nasal decongestants are sympathomimetics and cause vasoconstriction [25]. Concerns about the conversion of pseudoephedrine to the recreational drug methamphetamine have led to restrictions on the availability of common cold medicines containing pseudoephedrine. This has led to the substitution of pseudoephedrine with phenylephrine in many common cold products despite there being some debate about the efficacy of phenylephrine as a nasal decongestant [4].

Long-term use of topical nasal decongestants (over months or years) may cause nasal irritation and rhinitis medicamentosa [31]. The development of rhinitis medicamentosa is sometimes explained on the basis of nasal rebound congestion after use of topical nasal decongestants, with the patient continuing to use the nasal decongestant to treat congestion caused by use of the decongestant [32]. The nasal irritation and rhinitis induced by topical nasal decongestants may be due to the presence of preservatives such as benzalkonium rather than due to a pharmacological action of the medicine [32].

Conclusions

The topical nasal decongestants oxymetazoline and xylometazoline are safe and effective decongestants, but some caution is needed with any long-term use due to the development of rhinitis medicamentosa. The oral decongestants pseudoephedrine is less effective than the topical decongestants, and the efficacy of phenylephrine as an oral decongestant in OTC doses is debatable.

Antitussives

Cough is a vital reflex to protect the airway from aspiration of food and fluid but cough associated with common cold is disturbing and usually of no benefit. Even in cases of chesty productive cough when cough is important as a means of clearing the airway of mucus, excessive coughing may be debilitating. Antitussives can be used to decrease the frequency and inten-

sity of cough to provide symptom relief without abolishing the protective cough reflex.

Medicines

Almost all cough medicines are formulated as sweet syrups and this maybe related to the powerful placebo effects of a sweet taste on cough [33]. The sweet taste of honey may explain the traditional use of honey to treat cough and its efficacy as an antitussive [34].

Pharmacology

The antitussives may be divided into opiates such as codeine, opiate derivatives such as dextromethorphan and pholcodine, and sedating antihistamines such as diphenhydramine. Antitussives are believed to act by an inhibitory action on the brainstem areas that control cough. The opiates and dextromethorphan may have some specific effects on the brainstem area, whereas the antihistamines may only act as sedatives.

Efficacy

The efficacy of OTC antitussives has proven difficult to determine as there is no generally accepted method of determining efficacy and there is no generally accepted gold-standard antitussive to validate methods [35, 36]. Some authors doubt if any of the antitussive medicines are superior to placebo treatment with a sweet syrup [33, 34, 37, 38]. Meta-analysis of studies provides some limited support for the efficacy of dextromethorphan [39] but other studies demonstrate no superiority above placebo [34, 40]. In all acute cough studies there is a large placebo response and this makes it difficult to determine the efficacy of any pharmacologically active ingredient in an antitussive treatment. The large placebo response and rapid decline in cough severity after treatment with a cough medicine illustrated in Figure 4 is typical of this type of study. Cough associated with common cold may be under voluntary control and related to a sensation of airway irritation [41, 42], and this is another problem in conducting clinical trials as subjects may control cough according to their expectations about the efficacy of any medicine. Any unblinding of the study or side effects of an active treatment may influence voluntary control of cough and complicate the interpretation of cough clinical trials.

An explanation of the variability in antitussive response to dextromethorphan is that differences in the rate of metabolism of the drug between individuals cause much variability on the response to dextromethorphan [43]. There are few studies on the antitussive efficacy of sedating antihistamines,

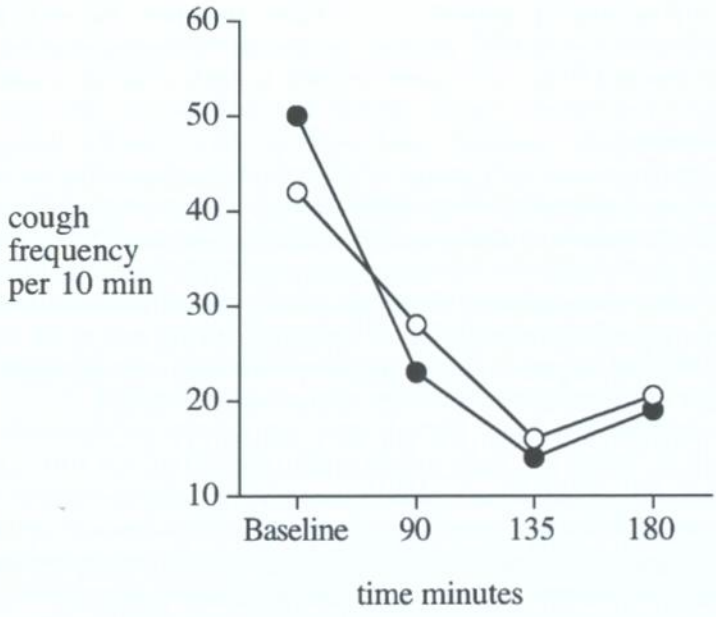

Figure 4. Median cough frequency (per 10 minutes) for patients with cough associated with common cold. Immediately after the baseline measurement (0 minutes) patients were treated with either a single dose of 30 mg dextromethorphan powder in a hard gelatin capsule (filled symbols, $n=21$), or a matched placebo capsule containing lactose powder (open symbols, $n=22$) [40].

pholcodine and codeine, and little support for any efficacy in the treatment of acute cough [36, 38, 44, 45]. Reviews provide no good evidence for the efficacy of OTC cough medicines [46].

Safety

The antitussive medicines, because of their effects on the central nervous system, are dangerous in overdose, especially in children [44, 47] and their central effects may be utilised for recreational abuse [48]. The recreational abuse of dextromethorphan has led to restrictions on the availability of this medicine in several countries [2, 3] and this trend is likely to continue.

Conclusions

There is only very limited support for the efficacy of OTC antitussives, especially in children, and since simple sweet syrups can provide relief of cough

without any antitussive medicine it is difficult to defend the inclusion of antitussive medicines in OTC products on any safety-benefit analysis.

Antihistamines

The first generation of sedating antihistamines were developed as specific histamine antagonists for the treatment of allergic reactions. The use of antihistamines as common cold treatments developed from a mistaken idea that common cold symptoms were due to an allergic type of response involving histamine. The allergic mechanism of symptoms was shown to be false in 1950 [49, 50] but the use of antihistamines as common cold medicines persists to this day because of useful side effects such as sedation.

Medicines

The antihistamines (diphenhydramine, chlorpheniramine, brompheniramine, doxylamine, triprolidine, promethazine, carbinoxamine) are used in a very wide range of medicines both as syrups and tablets for multi-symptom relief of cough, runny nose and sneezing, in combination with analgesics, decongestants, antitussives, and expectorants.

Pharmacology

The first generation antihistamines are useful as treatments because of their sedative and anticholinergic properties. The sedative actions make them useful as night-time treatments and antitussives, and the anticholinergic properties may help in the control of nasal secretions and sneezing [51, 52]. There is no support for the efficacy of newer non-sedating antihistamines in the treatment of common cold symptoms and this is probably because of the more specific antihistamine effect and lack of sedation and anticholinergic effects [50, 53].

Efficacy

The antihistamines were introduced as some of the first commercial common cold treatments in the 1940s before the advent of placebo-controlled trials, and although there are a few placebo-controlled studies supporting the efficacy of antihistamines as antitussives and antisecretory medicines, the evidence base is weak [44, 52, 54–56]. There is no doubt that the antihistamines are sedative, and this is a benefit for night-time medicines but an unwanted side effect for day-time use. There is some support for use of antihistamines in controlling runny nose and sneezing [52, 57].

Safety

The central sedative effect of the first generation antihistamines is a problem, especially in overdose, and because of the relative lack of evidence to support efficacy, some authors have proposed that antihistamines should be withdrawn from all OTC products [44]. However, this may be an extreme point of view as the antihistamines are widely used in OTC common cold products with relatively few adverse events when taken as directed.

Conclusions

The antihistamines survive as common cold treatments because of their sedative and anticholinergic effects rather than any effect on histamine. There is some support for their use as treatments for runny nose and sneezing but the sedative actions limit their usefulness. Use in children is difficult to support.

Expectorants

Expectorants are used to aid in the clearance of mucus from the bronchi in the lungs by making the mucus more fluid so that it is easier to clear by coughing. Expectorants such as ipecacuanha, squill and guaicol derivatives are probably the oldest surviving OTC treatments with a long history of various medical uses.

Medicines

Expectorants are usually taken as syrups to treat a 'chesty' or 'productive' cough. Medicines such as ipecacuhna, squill and guaicol have been used for centuries to treat coughs and colds. Squill was included in the first edition (1618) of the London Pharmacopoeia [58], and the history of guaicol as a medicine originates as an import from the new world in the early 17th century [59].

Pharmacology

The expectorants ipecacuhna, squill, guaicol and guaiphenesin are believed to act as gastric irritants and by means of a gastro-vagal reflex they stimulate airway secretions [60, 61]. The expectorants were first used in medicine as emetics to relieve the body of excess fluid that was believed to be the cause

of rhinorrhea and cough. Gunn (1927) [60] states that "A large number of drugs which have no common pharmacological property, other than that of being gastric irritants have in the course of time come to be used empirically as secretory expectorants when given by mouth. Many of these drugs have been used as emetics in larger doses". Ammonium salts may also work by means of gastric irritation and the mode of action of expectorants such as bromohexine is not known. Iodide salts may work *via* gastric irritation or alternatively, iodide may be secreted into airway mucus to alter the properties of the mucus, but the mode of action is unclear [61].

Guaiphenesin is a synthetic derivative of guaicol and is believed to act as a gastric irritant, although the mode of action is not known and there may be other effects of guaiphenisin such as antitussive activity [62].

Efficacy

There is little evidence that expectorants have any effect on cough and mucus composition in common cold. Most studies on expectorants have studied chronic cough rather than acute conditions such as common cold and even here there is little support for any beneficial effect [61, 63]. Some studies report a decrease in the viscosity of airway secretions associated with treatment with guaiphenesin during cough associated with colds [64, 65] but these studies have not yet been confirmed by other investigators.

One major problem in studying the efficacy of an expectorant is that there is no generally agreed method to assess efficacy [66] and that expectoration of saliva can complicate measurement of sputum viscosity and volume. Reviews on efficacy of expectorants in OTC cough medicines do not provide any support for this treatment [46].

Safety

The small number of clinical trials on expectorants do not raise any safety issues and the widespread use of these products over many years does support safety.

Conclusions

Expectorants are widely used in OTC medicines for the treatment of chesty cough associated with common cold but the lack of efficacy data to support this mode of treatment means that their use as a common cold treatment is not clearly proven.

Mucolytics

Mucolytic medicines are believed to alter the composition of mucus and make it more fluid and thus aid expectoration. The most widely used mucolytics are ambroxol, N-acetylcysteine and carbocysteine and, although the mode of action of these medicines is not fully understood, they are believed to alter the physical properties of mucus in this manner. There are only limited data that mucolytics provide any benefit in chronic pulmonary disease, and in this condition their efficacy is assessed over months rather than weeks or days [67, 68]. There is no clinical data to support the efficacy of mucolytics as expectorants in acute respiratory infections such as common cold but one study does indicate that ambroxol may help to prevent colds [69].

Menthol

Because of the popularity of menthol products this ingredient is discussed as a separate section, although it does not form a specific class of ingredients. Menthol and other plant aromatic oils such as eucalyptus and camphor have been used as treatments for colds in traditional remedies for centuries. Menthol has been used in vaporubs since the development of 'Vicks VapoRub' in 1890 [70]. Menthol is probably the most commonly used ingredient in common cold medicines. Menthol is often combined with camphor, eucalyptus and other aromatic oils, especially in vaporubs and inhalants and this sometimes makes it difficult to determine the efficacy and safety of the separate ingredients of the medicine. Only menthol is discussed as there is very little literature on the effects of the other aromatic oils on common cold.

Medicines

Menthol is a very versatile medicine as it is used in vapour rubs, lozenges, cough syrups, decongestant nasal sprays, throat sprays, aromatherapy oils, and even bath oils and shampoos. The typical smell of menthol is so commonly associated with cold medicines that it is often referred to as a 'Vicks' smell. Menthol is not always declared as an active ingredient in cold medicines and this sometimes makes it difficult to conduct a clinical trial to demonstrate efficacy of the declared active ingredient as both the placebo control and active medicine will contain menthol, and the menthol will relieve symptoms of common cold. The popularity of menthol-containing confectionery that may also be used as treatments for cold symptoms may be due to the effects of menthol on thirst and because of its mild stimulant effect [71].

Pharmacology

Menthol acts on temperature receptors in skin and mucosal surfaces to cause a sensation of coolness or warmth [72]. The cooling sensation is believed to be mediated by a transient receptor channel (TRPM8) located on the cell membrane of thermoreceptors on sensory nerve endings [73]. Menthol, cooling agent Icilin and cool temperature have all been shown to activate TRPM8 to cause an increase in intracellular calcium and generation of an action potential in the thermoreceptor sensory nerve ending [73]. The interaction with TRPM8 has some similarity to interaction with a specific pharmacological receptor as there are differences in the efficacy of different menthol isomers in inducing the sensation of coolness [74, 75]. L-Menthol has the greatest cooling activity and the stereo isomer D-menthol has little cooling activity [74, 76].

Menthol is used in vaporubs, lozenges, and nasal sprays to relieve the sensation of nasal stuffiness associated with colds, and this effect is brought about by stimulation of cold receptors in the nose [77, 78]. Menthol lozenges are monographed by the FDA as effective cough drops and menthol may influence cough by acting on airway sensory nerves or smooth muscle [79]. Although menthol is claimed to have a bronchodilator action there is little support for this effect [80].

Efficacy

Inhalation of menthol vapour on sucking a menthol lozenge causes a sensation of improved airflow due to a cool sensation in the nose, without any objective change in nasal airway resistance as illustrated in Figure 5 [78]. Menthol vapour can relieve symptoms of nasal congestion but is not a nasal decongestant. In high concentrations menthol acts as an irritant and may cause nasal congestion [81, 82].

Menthol is a common ingredient in cough medicines but there is little support for efficacy as an antitussive. Studies on citric acid-induced cough in healthy adult subjects provide some support for an antitussive effect [83], but this has not been confirmed in a similar study on children [80].

Menthol is a common ingredient in lozenges for treatment of sore throat and the local anaesthetic action of menthol may be beneficial in this form of treatment [75]. Despite the widespread use of menthol in throat lozenges, no support has been found in the literature for the use of menthol to treat sore throat apart from a recommendation in 1890 [84].

Topical application of menthol in peppermint oil or balm to the forehead has been shown to relieve headache [85, 86].

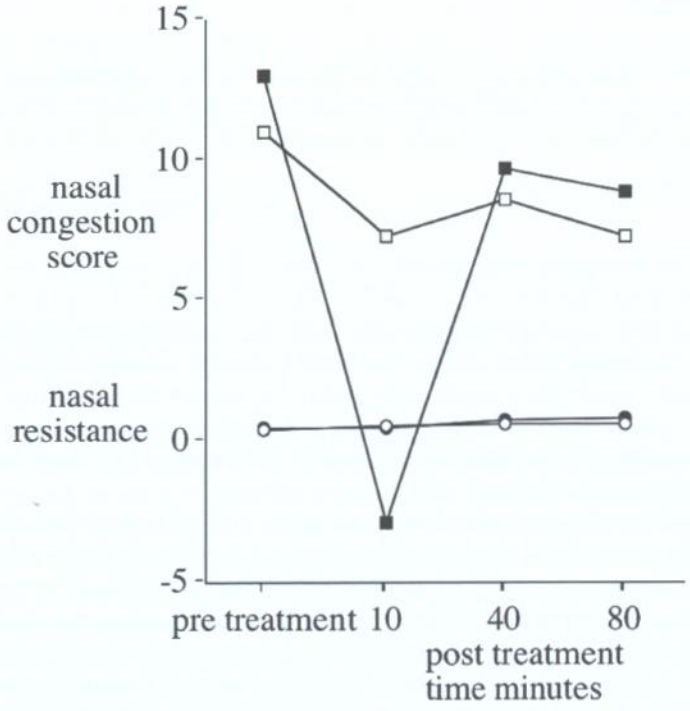

Figure 5. The effects of ingestion of an 11 mg L-menthol lozenge on subjective sensation of nasal congestion and nasal resistance to airflow in human volunteers with common cold. The subjective sensation of nasal congestion, measured on a 100-mm visual analogue scale, was significantly reduced 10 minutes after ingestion of the lozenge but nasal airway resistance as measured by rhinomanometry was unaffected. Shaded symbols represent the values for the menthol-treated group and the open symbols represent the mean values for the placebo-treated group. Results taken from [78].

Safety

Menthol-containing medicines in a wide range of topical and systemic medicines have been used for over a hundred years in the treatment of common cold and there are few reports of any adverse events attributed to menthol. Vaporubs and other menthol-containing medications are used on infants and there are concerns that high concentrations of menthol applied close to the nose may cause apnoea in susceptible infants [87, 88]. However, when used as directed, vaporubs may ease breathing in infants with acute bronchitis associated with common cold [89].

Conclusions

Menthol is a safe and effective medicine for relief of symptoms of nasal congestion, cough, headache, and sore throat pain. It is formulated in a wide range of medicines and is probably the most popular treatment for common cold.

Sore throat lozenges and sprays

Sore throat or acute pharyngitis is a common problem associated with common cold and there is a large market for medicated confectionery and throat sprays to provide symptomatic relief for this condition. Many of the so-called 'throat drops' contain menthol, and the mild local anaesthetic action of menthol and demulcent effect of the lozenge [75] may provide some relief from sore throat.

Medicated lozenges often contain an antiseptic (chlorhexidine, dequalinium, hexylresorcinol, amylmetacresol, bichlorbenzyl alcohol, cetylpyridinium chloride) and they often claim antibacterial activity as a therapeutic benefit in treating sore throat. The antiseptics do have antibacterial activity when tested *in vitro*, and this antibacterial action may also be shown in the oral cavity, but it is doubtful if any antibacterial activity is useful in treating sore throat, as most throat infections are caused by viruses [90]. There is no clinical or scientific support for the use of antiseptics in the treatment of sore throat, but the public perception of the usefulness of antibacterials in this condition persists in much the same way as the demand for antibiotic prescription for sore throat, despite the fact that there is no evidence that antibiotics provide any benefit [91].

Sore throat sprays and lozenges containing a local anaesthetic agent (lidocaine, benzocaine) may provide relief from sore throat pain [92] but they do have a numbing effect on the tongue that affects taste, and this side effect may limit the tolerability of the sprays.

Placebo effect

OTC medicines for the treatment of common cold may provide the greatest benefit to the patient by means of a placebo effect. Because of safety issues in OTC medicines that are freely available to the public, the active pharmacological ingredient in cold medicines is often at the level of the minimal effective dose. In cough medicines it has been proposed that 85% of the benefit of the medicine is due to the placebo effect of the medicine and only 15% is contributed by the antitussive medicine [37]. The placebo effect is related to the patients' belief in the efficacy of the medicine and this may be enhanced by the 'brand' of the medicine and advertising [93]. The pla-

cebo effect is not just a psychological effect as placebo treatment may cause physical changes in the body such as effects on the immune system [94]. In this respect, the faith in a medicine and the subsequent placebo effect may influence the course of a common cold illness [95].

Multi-symptom treatments

Multi-symptom treatments that contain several medicines to treat several symptoms simultaneously are popular with consumers but are viewed critically by some pharmacists and clinicians. The consumers like the multi-symptom treatments because they provide a cheap and safe way of treating multiple symptoms with what is viewed as a single treatment. However, the medicines may be criticised as exposing patients to one of the ingredients when they do not have all the symptoms that the multi-symptom medicine is proposed to treat. Common combination medicines are analgesic plus decongestant, and a triple therapy may include a sedating antihistamine to control cough or runny nose and sneezing. In some cases the multi-symptom treatment may contain four active ingredients (paracetamol, dextromethorphan, doxylamine, and ephedrine and there is some support for the efficacy of this mix as an effective and convenient therapy for multiple symptoms [96].

Common cold symptoms usually occur as a complex of multiple symptoms [97] and therefore it is reasonable to develop multi-symptom medicines to conveniently treat the symptom complex, even if on some occasions there may not be a need for all of the medicines in the treatment.

Hot drinks

Despite the widespread folklore that hot drinks are an effective treatment for colds and flu, and the use of hot drink formulations for many current common cold OTC medicines, there is little evidence base in the medical literature supporting the efficacy of a hot drink for common cold and flu. A study investigated the effects of a hot fruit drink on objective and subjective measures of nasal airflow, and on subjective scores for common cold/flu symptoms in 30 subjects suffering from common cold/flu [98]. The results demonstrated that the hot drink had no effect on objective measurement of nasal airflow but it did cause a significant improvement in subjective measures of nasal airflow. The hot drink provided immediate and sustained relief from symptoms of runny nose, cough, sneezing, sore throat, chilliness and tiredness as shown in Figure 6, whereas the same drink at room temperature only provided relief from symptoms of runny nose, cough and sneezing. The effects of the drinks on symptom relief may be explained in terms of a placebo effect and physiological effects on salivation and airway

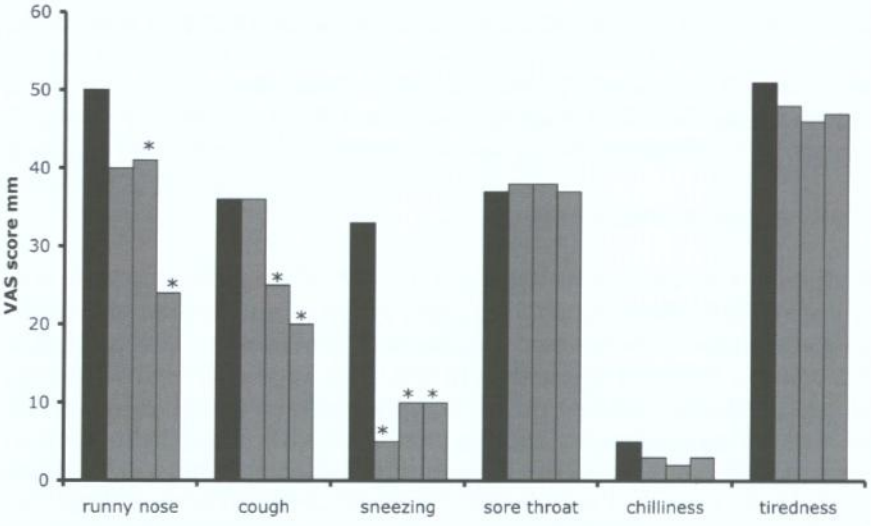

Figure 6. Effects of a hot fruit drink on common cold symptoms scored on visual analogue scales (0 = no symptom, 100 = worst symptom I can imagine). Each bar represents the median value of data from 15 subjects, for baseline (dark), and 10, 15 and 30 minutes after the drink. Statistically significant differences from baseline ($p < 0.05$) are indicated by an asterisk [98].

secretions [33], especially for relief of sore throat and cough symptoms where promotion of salivation will lubricate inflamed mucosal surfaces.

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