

OVERVIEW – RISK: BENEFIT OF OTC COUGH AND COLD MEDICINES IN CHILDREN

1. INTRODUCTION

Following concerns about the safety of over-the-counter (OTC) cough and cold medicines in young children which were initially raised in the USA, the purpose of this review is to evaluate all available evidence on risk:benefit relevant to UK use.

There are four main categories of pharmacologically active ingredients used in children's cough and cold medicines authorised in the UK for sale without prescription (OTC): nasal decongestants (pseudoephedrine, ephedrine, phenylephrine, oxymetazoline and xylometazoline), expectorants (guaifenesin and ipecacuanha), antitussives (dextromethorphan and pholcodine); and antihistamines (diphenhydramine, chlorphenamine, brompheniramine, promethazine, triprolidine and doxylamine).

Actives from the four categories are commonly used in combination with actives from the other categories or other actives (many preparations also contain analgesics) to treat a variety of symptoms of the common cold. Antihistamines are used almost entirely in combination, most commonly with decongestants or antitussives and in some cases both. Combination expectorant and decongestant preparations are also currently authorised in the UK.

2. SOURCES OF EVIDENCE

Data supplied by Marketing Authorisation Holders (MAHs) – following a request from the MHRA to provide data - have been reviewed. Available data from the published literature, UK spontaneous suspected adverse reaction reports, National Poisons Service data and Hospital Event Statistics (HES) data have been reviewed. Assessments and reviews from other regulatory authorities have been reviewed.

3. BACKGROUND

3.1 UK Regulatory History

Following an application from a MAH to remove the licensed indication, and dosages, for children under two years of age, in February 2008 the Paediatric Medicines Expert Advisory Group (PMEAG) and the Commission on Human Medicines (CHM) advised that the risk to benefit balance associated with OTC cough and cold medicines for use in the paediatric population under 2 years was no longer favourable. In addition, PMEAG and CHM advised as an interim that products authorized for children aged 2-6 years should be updated to include: information on maximum daily dose; a warning not to take with any other cough and cold medicines; and instruction to seek the advice of a pharmacist or other healthcare professional before using the medicine. Single-constituent paracetamol and ibuprofen products were not affected.

Following a publication in April 2008 detailing adverse drug events from cough and cold medications in children in the US, PMEAG were updated in June 2008. PMEAG recommended that MAHs should be required to submit data to demonstrate a positive risk:benefit of the authorised products. In addition, as a risk minimisation strategy PMEAG considered that all OTC cough and cold medicines licensed for use in children be supplied in child-resistant containers (CRCs) with appropriate dosing devices, as well as guidance for parents and healthcare professionals on the appropriate management of cough and cold symptoms.

3.2 International Regulatory Activity

3.2.1 USA

In the USA most OTC cough/cold medications are marketed under the authority of the formal OTC "monograph" system rather than as individual marketing authorisations. Amendment of a monograph involves writing a new regulation and may take some years to implement. The FDA is in the process of developing a proposed rule to revise the paediatric labelling contained in the *Final monograph for cough, cold, allergy, bronchodilator and antiasthmatic drug products for Over-the Counter human use* and held a public meeting to obtain input regarding this process, including input on what studies should be conducted to assess effectiveness and /or safety, if they should still be available OTC and how should age be considered in making regulatory decisions. Public consultation will be undertaken in 2009.

Although no regulatory action has been taken – the FDA review is still ongoing - most manufacturers in the US have voluntarily amended product warnings to state ‘do not use in children under 4 years of age’ and, for antihistamine products, added a warning that they should not be used as a sedative has been included. In addition, manufacturers in the US are conducting pharmacokinetic studies on 8 actives: phenylephrine, diphenhydramine, pseudoephedrine, chlorphenamine, brompheniramine, dextromethorphan, guaifenesin and doxylamine.

3.2.2 Canada

Further to its recommendation in 2007 that these products should not be used in children under 2 years, Health Canada has announced that all oral cough and cold products should state ‘not to be used for children under 6 years’ on the label. This recommendation takes into account the following factors:

- I. Recommendations from Canadian and international health professionals and experts that these medicines should not be used in children under 6;
- II. Body weight and its effect on how medicines work. Some children between the ages of 2 and 6 years may weigh the same as other children who are less than two years old, the most vulnerable group;

- III. Children under the age of 6 years generally have more colds compared to older children and therefore, are likely to be exposed more frequently to these medications; and
- IV. Younger children are less likely to be able to communicate a potential side-effect from a cough and cold medicine and to ask their parents/caregivers for help in the same way a child over the age of 6 can.

For children aged 6 to 12 years Health Canada has introduced a number of restrictions including strengthened warnings and requirements for child resistant packaging and dosing devices.

4. COUGHS AND COLD IN CHILDREN

4.1 Incidence of Cough and Cold in children

Children get more coughs and cold than adults. The frequency decreases with age as the immune system develops. Estimates reported in the Lancet (Heikkinen & Jarvinen, 2003) suggest that on average children under 1 year in the UK get about 6 colds a year, children 1-2 years get 5.7, 3-4 year olds get 4.5 and 5-9 year olds get 3.5 colds per year. Other groups have estimated that children under 6 years get between 6-8 coughs a year with the number diminishing around 6 years (Taylor, 1992).

4.2 Use of cough and cold products in children in UK

There is a high propensity for parents and carers to treat the symptoms of cough and cold in children. A recent US publication reporting the results of the Slone survey (Vernacchio et al, 2008) revealed that in a given week a cough and cold medication was used by 10.1% of US children. Exposure was highest to decongestants and first generation antihistamines, followed by antitussives and expectorants. Multiple-ingredient products accounted for 64.2% of all cough and cold medications.

From data provided by the Propriety Association of Great Britain (PAGB) it is estimated that over 55 million packs of cough and cold medications with indications for children under 12 years are sold in the UK each year and 12 million packs are sold with indications authorised for children less than 6 years of age. This is in the context of an estimated UK population of under 6 year olds of 3.6 million.

For products authorised for use in children aged under 6 years the most widely purchased products are preparations containing expectorants (7.6 million), followed by antihistamines (3.4 million), antitussives (2.3 million) and decongestants (1.9 million). As most products are authorised for use in a range of age groups, including adults, these figures do not necessarily reflect the relative usage of the different products in children.

5. BEST PRACTICE FOR TREATING COUGH AND COLD

Current NHS/Department of Health (DH) advice on treating colds and coughs in children includes giving fluids and treating fever and pain with paracetamol or ibuprofen, and the use of saline drops to loosen dried nasal secretions or help a stuffy nose in young children and babies. Although steam inhalation is not suitable for children because of the risk of scalding, a child may benefit from sitting in a hot, steamy bathroom. Simple cough mixtures containing a demulcent, for example glycerin, and syrup can have a soothing effect by coating the throat and relieving the irritation which causes the cough; a child over the age of one may also be helped by a warm drink of lemon and honey. If a cough as a result of a viral infection does not go after 2 weeks a doctor should be consulted.

With respect to the use of cough and cold medicines the DH publication *Birth to Five* states that cough and cold medicines have not been shown to work and may produce side-effects in young children and may cause poisoning if a child accidentally swallows more than the recommended dose. However, despite this many parents and carers often feel the need to treat a child with an OTC cough and cold medicine. It is therefore important these medicines are used appropriately in order to minimise any risk.

It is important that parents have information on the appropriate preparations for the child's symptoms: cough suppressants should only be used to treat a dry cough; antihistamine preparations should not be used if the child does not have a runny nose and should not be used to sedate a child; and expectorants are appropriate only for a chesty or productive cough. Specific warnings and precautions for the individual preparations should be followed, including in relation to duration of use.

The label (and leaflet) should always be read and dosage advice appropriate for the child's age should be followed using the measuring device made for the medicine.

6. EVIDENCE

The reviews of the available safety and efficacy evidence for the ingredients in the four drug categories are summarised below:

6.1 *Safety and Efficacy*

Previous (Cochrane) reviews have concluded:

“There is insufficient data on the use of [nasal decongestants] in children and therefore they are not recommended for use in children younger than 12 ...”

and

“There is no good evidence for or against the effectiveness of OTC medicines in acute cough ... it remains unclear whether these medications are helpful ...”

Very few trials have been conducted in children to current standards: a total of 38 clinical trials were considered for this review - these trials contain design faults which may have limited their ability to detect differences between treatment and control groups.

There are no robust data providing convincing evidence of efficacy for any of the active ingredients – alone or in combination – in the treatment of cough and cold symptoms in children. A summary of the evidence of efficacy and safety for each of the four main categories reviewed is set out below.

6.1.2 Sympathomimetic Nasal Decongestants

Efficacy

There are severe limitations to the efficacy studies given that many of the products were first introduced decades ago. There has been no co-ordinated development program to establish efficacy. What trials there are have not been carried out to current standards. Many of the studies had populations of mixed ages (ie included adults and children). Many studies evaluated the relief of nasal congestion in other conditions associated with nasal stuffiness as well as the common cold. Standardised and validated objective measures were not used and subjective symptoms of nasal stuffiness often do not correlate with objective measures. Many of the studies were of multi-ingredient products, seriously limiting the evaluation of the effect of single agents.

There is one inconclusive study of multiple-dose single-constituent pseudoephedrine in the common cold in children/adolescents aged 2 to 16 years. Otherwise, there are no adequately designed studies of the sympathomimetic nasal decongestants in this patient population, so a favourable benefit to risk cannot be established.

Safety

From the 5 sympathomimetic nasal decongestants, there were 138 serious reactions in children under the age of 12 years reported in the UK, with 3 of these classified as overdose. For children of 6 years and under, there were 89 serious reactions with 3 of these reported as overdose (ie all the overdoses were in the younger age group as were 2/3^{rds} of the reactions).

6.1.3 Expectorants

Efficacy

No studies appeared to have investigated the effect of single-constituent guaifenesin in acute cough in children, and 3 published studies in non-acute cough in children failed to show any effect of guaifenesin. Sixteen published studies in adults (including 1 in adults and children) were reviewed, which examined the effect of guaifenesin (alone or in combination with other substances) on endpoints including acute cough, non-acute cough and sputum viscosity or properties. These studies had mixed results but some provided evidence of efficacy of guaifenesin in adults, in terms of easing of expectoration. Unpublished data were also reviewed but did not provide any additional robust evidence of efficacy of guaifenesin.

No studies appeared to have investigated the efficacy of ipecacuanha in acute cough in any age group.

Safety

In the MHRA ADR database there are 78 serious reports associated with expectorants in children aged under 12 years: 55 in children under 6 years and 23 in children aged 6-12 years. Two cases were associated with accidental overdose, both in children under 6 years.

6.1.4 Antitussives

Efficacy

Overall, ten studies investigating antitussives in the treatment of acute cough in children were identified. There were 8 studies reviewing the efficacy of dextromethorphan (DXM) in the paediatric population. Only 3 of them reported a variable degree of positive effect on the symptom scores; however, it is important to note that there were issues with the design of the studies such as: definition and timing of treatment outcomes, adequacy of dose, dosing frequency, and duration of therapy. Additionally in 2 of the studies a combination drug was used and therefore it is unclear if the positive effect could be attributed to DXM. The other much newer studies all failed to show any effect of DXM in the treatment of acute cough, even when compared to honey.

Regarding pholcodine only 2 very old studies have been identified in the paediatric population. In these studies no placebo groups were included and in one of them a combination drug with paracetamol was used in patients aged 6 years and above. Both of the studies report a general improvement of the overall cough and cold symptoms as reported by parents without substantial details of the measured outcomes.

Safety

In the MHRA ADR database there are 14 unique reports of serious reports associated with dextromethorphan in children aged 12 years and under with a total number of 18 suspected serious reactions. The most frequently reported reactions relate to neuro-psychiatric disorders (7/18) and skin reactions (5/18). There has been no fatal case in UK.

For pholcodine there are 21 unique reports of serious ADRs in children aged 12 years and under. Overall there were 36 reported reactions equally distributed among the age groups (0-2y, 2-6y, 6-12y). Across the age groups, the most frequently reported reactions relate to neuro-psychiatric disorders (12/36) and skin reactions, including erythema, urticaria and rash (10/36). There were also 2 cardiac reactions in the very young and in the older age group and 6 respiratory reactions including asthma, bronchospasm and respiratory depression, across all age groups. A fatal report associated with pholcodine was received in January 2008. The original toxicology screen showed pholcodine at a level higher than expected for therapy, however this has been ruled out as a cause of death which was attributed to other causes.

6.1.5 Antihistamines

Efficacy

Five randomised–controlled trials investigating antihistamines in the treatment of cough and cold in children were identified. Only one trial reported a positive effect (with astemizole, a non-sedating antihistamine), however, the value of this study is limited as it appeared to include children who did not have the common cold and may have had symptoms of allergy instead. The other studies all failed to show any effect of antihistamines in the treatment of the common cold but these studies did have limitations which may have affected their ability to detect a difference between placebo and active treatment.

Safety

In the MHRA ADR database there are 127 serious reports associated with antihistamine cough and cold preparations in children aged under 12 years: 92 in children under 6 years and 35 in children aged 6-12 years. Only one case was associated with accidental overdose.

6.2.1 Suspected Adverse Drug Reactions - overview

The number of spontaneous suspected ADR reports for all groups is limited, but under-reporting would be expected with OTC medicines. The value of spontaneous reports is also limited as the frequency of adverse reactions cannot be established because of lack of denominator data, particularly in different age groups. It is also difficult to attribute causality as most of the reports are associated with multi-ingredient products and some reactions may be as a result of the underlying disease rather than as a result of the medicines.

The main patterns of reports relate to CNS adverse effects with the antihistamines, antitussives, and decongestants; and allergy/hypersensitivity reactions, particularly with the expectorants.

There have been serious suspected ADR reports in children, over 360 in children under 12 were identified as part of the review, the majority in children aged under 6 years, associated with cough and cold ingredients especially those containing pseudoephedrine, diphenhydramine, chlorphenamine and dextromethorphan; also, a small number of serious cases have been reported where guaifenesin was the only active substance. Some of these reports are not associated with overdose. In addition, there are reports of abuse, mainly from the US, Canada, and Scandinavia of dextromethorphan, alone or with other drugs, mainly by adolescents.

6.2.2 Hospital admissions

In England, data on hospital admissions and out-patient data are recorded by Hospital Event Statistics (HES) - though the majority of attendances at A&E are not captured by HES. In 2006/7 (the most recent data available) there were a total of 230 children in England aged under 14 who were admitted to hospital following exposure to antitussives, expectorants or common cold remedies (11 poisoning by antitussives, 39 poisoning by expectorants, 182 poisoning by anti-common-cold remedies). Taking into account population size the English data indicates a higher admission rate than in the US but this may be because criteria for admission may differ, given the very different healthcare systems, and the different age ranges (under 12 in US, under 14 in England).

6.2.3 National Poisons Information Service

Data have been provided by NPIS for the UK covering total calls annually from 2004 to 2007. The total number of calls for this 4-year period was 144,242. Data for the antihistamines, antitussives and cough suppressants are shown below:

	Total	Under 5 years	Under 9 years
Diphenhydramine	949	227 (24%)	255 (27%)
Chlorpheniramine	846	351 (41%)	431 (51%)
Ipecacuanha	28	15 (54%)	20 (71%)
Pholcodine	205	159 (78%)	165 (80%)
Dextromethorphan	284	116 (40%)	136 (48%)
Guaifenesin	376	255 (68%)	277 (74%)

6.2.4 Published literature

In April 2008 a study by the Centers for Disease Control and Prevention (CDC) analysing adverse drug events (ADEs) from cough and cold medication in children, based upon emergency department visits in the US, was published (Schaefer et al, 2008). The data suggest that annually approximately 7100 patients aged under 12 years were treated in emergency departments in the USA for ADEs from cough and cold medicines.

In summary, most visits were reported for children aged between 2-5 years (64%), with the majority of these being related to unsupervised ingestions (77%), however, a substantial minority (18%) related to non-overdose adverse events such as allergy. In contrast, for children aged less than 2 years almost half of the cases were due to excessive dosing by caregivers.

7. RISK/BENEFIT ANALYSIS FROM DATA REVIEWS

Overall, from the data reviews a favourable risk/benefit for any of the drug categories in the treatment of cold and coughs in children cannot be established.

As a favourable risk/benefit remains to be established in children it could be argued that cough and cold products should not be used in this age group. However, this could be seen as unnecessarily restricting availability of medicines in the absence of a significant

safety concern in older children and adults; and it arguably fails to take into account the extensive use, over many years, of these products.

Although there is some rationale for some combinations authorised in the UK the wide use of such products means that children may be exposed to actives they do not need for their particular symptoms; and the rationale for some combinations – such as those containing an antihistamine (which dry up and thicken respiratory tract secretions) and an expectorant (which is believed to make secretions easier to expel) - is illogical. More importantly, some combinations of active ingredients may potentially increase the risk of serious adverse reactions: for example, combinations containing both cough suppressants and antihistamines which both act centrally may carry an increased risk of CNS side-effects, such as hallucinations and convulsions.

8. DISCUSSION

The symptoms of cold are the body's natural defence against the virus. In some circumstances treatment of symptoms, even if effective, may not be desirable, since this could reduce the body's capacity to deal with the virus; this may be particularly pertinent in the case of suppression of the cough reflex in young children.

Dosage

Doses of these products, including fixed combination products, in children are based on extrapolation from adult doses which assumes that disease progression and clinical response in paediatric and adult populations are the same. Adjustments made on body weight alone may not be sufficient as children may exhibit different drug absorption and disposition compared with adults, particularly clearance which is a highly variable parameter in the paediatric population, which are likely to impact on the drug response. Few pharmacokinetic studies have yet been done on the drug categories in children and therefore effective doses in children remain to be established.

Efficacy

The reviews of the drug categories highlight the paucity of data regarding both efficacy and safety for cough and cold products in children; evidence of efficacy, in particular, is largely based on extrapolation from adult data where available and there are no robust data providing convincing evidence of efficacy for any of the active ingredients alone or in combination for treatment of cough and cold in children..

Safety – adverse reactions

In terms of safety, under-reporting of suspected adverse reactions is a well-recognised problem for all OTC medicines and particularly for long-established products. Serious reactions have been reported in the UK and US with therapeutic doses in children over the age of 2 years. Particular concern is raised about the number of serious reports associated, especially from the US, with dextromethorphan at normal doses. The growing problem of abuse of dextromethorphan is also a concern.

In addition, the pharmacology of some of the actives, particularly suppression of cough in young children, raises concern. As many preparations contain combinations of actives this potentially increases the risk of serious side-effects. For example, the risk of CNS side-effects could be increased with two centrally acting actives such as with cough suppressant/antihistamine combinations.

Overdose

Available data show that young children are particularly sensitive to the effects of overdose and this appears to account for the majority of adverse reactions reported in the US. In addition, as illustrated in the CDC article, unsupervised ingestions peak around the age of 3 years. Available UK data indicate that in the UK a significant number of children are admitted to hospital following an overdose.

Risk from overdose and in normal use must both be considered in the context of treatment of the symptoms of a self-limiting condition. It is important to note that ineffectiveness of products could increase the likelihood of inappropriate use of these medicines as parents and carers may be more inclined to overdose if the first dose given has had no effect on the symptoms.

9. EXPERT ADVICE

The Commission on Human Medicines (CHM) - the Government's independent expert advisors – concluded that:

- There is no robust evidence that cold and cough medicines containing the above ingredients work. Given that there have been some reports of harm with these ingredients, the risks of cough and cold medicines containing them outweigh the benefits;
- For children aged over 6 years, the risk from these ingredients is reduced because: they suffer from cough and cold less frequently and consequently require medicines less often; with increased age and size, they tolerate the medicines better; and they can say if the medicine is working. For these reasons cold and cough medicines containing the above ingredients can continue to be available for these older children, but only through pharmacies;
- Further research is required on how effective these products are in children over 6 years.

The CHM advised that:

- Cough and cold medicines containing the ingredients reviewed should not be used in children under 6.
- Cough and cold medicines for 6 to 12 year olds containing the ingredients reviewed will continue to be available in pharmacies, with clearer advice on the packaging/labelling and from the pharmacist.

- Products for children of 6 to 12 years containing the ingredients reviewed should be indicated for use “second line” to standard best care, and with duration of use restricted to no more than five days.
- Cough and cold medicines for 6 to 12 year olds should have strengthened warnings on the packaging and labelling.
- All liquid cough and cold medicines (including those for adults) should be supplied in a child resistant container.
- Certain combinations (such as cough suppressants and expectorants) should be phased out.

10. MHRA ACTION

On 28 February 2009 the MHRA announced the comprehensive package of measures set out in the advice from the CHM. These are available on the MHRA website:

<http://www.mhra.gov.uk/Safetyinformation/Safetywarningsalertsandrecalls/Safetywarningsandmessagesformedicines/CON038908>

The MHRA is working with industry and healthcare professionals to encourage ‘best practice’ and implement these measures. Industry has agreed to implement changes over a period of time. They will make the necessary labelling changes to state that these medicines should not be used in children under 6, introduce updated labelling, and change the legal status of medicines authorised for children aged 6 – 12 years from general sale (GSL) to pharmacy (P).

Newly labelled products will start to appear for the 2009 cough and cold season. Medicines with the old labelling will not be cleared off shelves. This is because many of these products are used in adults and children, and so cannot be withdrawn, creating a shortage of these medicines. Withdrawing these medicines would not be proportionate compared to the risk of side effects.

These changes should be completed by March 2010, except that the move towards ensuring all liquid cough and cold medicines (including those for adults) are supplied in a child resistant container will be implemented longer-term.