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Methylxanthines for prolonged non-specific cough in children (Review)

Chang AB, Halstead RAP, Petsky HL

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[Intervention Review]

Methylxanthines for prolonged non-specific cough in children

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ABSTRACT

Background

Non-specific cough is defined as non-productive cough in the absence of identifiable respiratory disease or known aetiology. It is commonly seen in paediatric practice. These children are treated with a variety of therapies including a variety of asthma medications. Methylxanthines, the main medication used for paediatric asthma for many decades in Western countries, is still widely used in non-Western countries. Also, methylxanthines have other pharmacological properties and their bronchodilator effect is only modest.

Objectives

To evaluate the efficacy of methylxanthines in treating children with non-specific cough.

Search methods

The Cochrane Register of Controlled Trials (CENTRAL), the Cochrane Airways Group Specialised Register, MEDLINE and EMBASE databases were searched by the Cochrane Airways Group. The latest searches were performed in October 2010.

Selection criteria

All randomised controlled trials comparing methylxanthines with a placebo medication in treating children with non-specific cough.

Data collection and analysis

Results of searches were reviewed against pre-determined criteria for inclusion. No eligible trials were identified and thus no data were available for analysis. Four small non-randomised controlled trials were reported.

Main results

No randomised controlled trials that examined the efficacy of methylxanthines in the management of prolonged non-specific cough in children were found. In the non randomised trials above, a significant effect was seen within 2-14 days of therapy.

Authors' conclusions

There is currently an absence of reliable evidence to support the routine use of methylxanthines for symptomatic control of non-specific cough in children. If methylxanthines were to be trialed in children with prolonged non-specific cough, cohort data (thus limited) suggest a clinical response (subjective cough severity) would be seen within two to five days (and certainly within 14 days) of therapy. However

methylxanthine use has to be balanced against the well known risk of toxicity and its low therapeutic range in children. Further research examining the efficacy of this intervention is needed.

PLAIN LANGUAGE SUMMARY

Methylxanthines for prolonged non-specific cough in children

Children with non-specific cough (dry and non-productive cough without any other respiratory symptom, sign or systemic illness) are commonly treated with a variety of medications to manage the symptom of cough. This review examined whether there was any evidence for using methylxanthines in children with non-specific cough. There were no randomised controlled trials that assessed methylxanthines for prolonged non-specific cough in children. In four non-randomised controlled studies, the researchers described that dramatic improvements in cough were seen within 2-14 days of taking oral theophylline. However, this is possibly a placebo and/or time period effect. There is no RCT evidence to support the routine use of methylxanthines for the symptom of non-specific cough in children. Further research examining the effects of methylxanthines using child appropriate cough outcome measures are needed.

BACKGROUND

Cough is the most common symptom presenting to general practitioners (Britt 2002; Cherry 2003) and causes significant anxiety to parents (Cornford 1993). Worldwide the desire to reduce the impact of the symptom of cough is reflected in the billions of dollars spent on over the counter cough and cold medications. Non-specific cough has been defined as non-productive cough in the absence of identifiable respiratory disease or known aetiology (Chang 2001). While some children with chronic non-specific cough have asthma, the majority do not (Chang 1999; McKenzie 1994).

Methylxanthines are pharmaceutically available as theophylline, aminophylline and caffeine. More recently, methylxanthine derivatives (pentoxifylline, propentofylline and pentiphylline) are used as neuro protective (Bath 2004) or vascular agents and not for diseases of the respiratory tract. Theophylline and aminophylline are currently the methylxanthines available for the respiratory tract. Currently, these medications are not commonly used in the majority of developed Western countries but are still widely used in the treatment of asthma in developing countries. In developed countries, before corticosteroids became the main therapeutic option for the management of paediatric asthma, these medications were previously extensively used in the management of asthma (Skoner 2002).

The frequently cited studies on 'cough variant asthma' in the 1970s and 80s used theophylline (amongst other agents that included major tranquillisers) (Chang 1999) which was the main therapeutic agent for asthma of the era (Skoner 2002). However, methylxanthines have many other pharmacological properties and their bronchodilator effect is only modest (Rabe 1998). The effects of methylxanthines on the respiratory tract include immunomodulation, decrease in diaphragmatic muscle fatigue, increase mucociliary clearance, and improvement of central hypoventilation (Rabe 1998; Vassallo 1998). Indirectly its potential respiratory benefits include an "increase in endogenous secretion of cortisol, stimulation of release of endogenous catecholamines; positive inotropic effect on the heart and as a mild diuretic" (Ram 2002). Thus methylxanthines may have an effect on abnormal cough that is separate to its modest bronchodilator effect. Indeed a randomised controlled trial in adults showed that theophylline decreased cough associated with ACE inhibitors (Cazzola 1993). Use of any medication has to be balanced against possible harm/ adverse events. The use of methylxanthines in children has been associated with impaired neuro-cognitive function in children (Skoner 2002) (although there is some controversy (Stein 1996)). Also, they have a narrow therapeutic range and toxicity effects including seizures. Methylxanthines also potentially impair the developing nervous system through its non specific inhibition on adenosine receptors (Millar 2004).

Thus although methylxanthines have a range of recognised benefits for the respiratory system (Rabe 1998) including a possible impact on cough, their associated adverse events needs to be considered. A systematic review of the benefits (or otherwise) of methylxanthines on chronic non-specific cough would thus be useful to help guide clinical practice.

OBJECTIVES

To evaluate the efficacy of methylxanthines in treating children with non-specific cough.

METHODS

Criteria for considering studies for this review

Types of studies

All randomised controlled trials comparing methylxanthines (theophylline, aminophylline, caffeine) with a placebo medication for cough, where cough is not primarily related to an underlying respiratory disorder such as cystic fibrosis, asthma, suppurative lung disease etc.

Types of participants

Children with chronic (> 3 weeks) non-specific cough (dry and non-productive cough without any other respiratory symptom, sign or systemic illness).

Exclusion criteria: cough related to mycoplasma, pertussis and chlamydia, presence of underlying cardio-respiratory condition, current or recurrent wheeze (> 2 episodes), presence of other respiratory symptoms (productive cough, haemoptysis, dyspnoea), presence of other respiratory signs (clubbing, chest wall deformity, respiratory noises such as wheeze on auscultation and other adventitious sounds), presence of any sign of systemic illness (failure to thrive, aspiration, neurological or developmental abnormality), presence of lung function abnormality.

Types of interventions

All randomised controlled comparisons of methylxanthines (theophylline, aminophylline, caffeine) with placebo. Trials only comparing two or more medications without a placebo comparison group were not included. Trials that included the use of other medications or interventions were included if all participants had equal access to such medications or interventions.

Types of outcome measures

Primary outcomes

Proportions of participants who were not cured or not substantially improved at follow up (clinical failure).

Secondary outcomes

1. Proportions of participants who were not cured at follow up,
2. Poportions of participants who not substantially improved at follow up,
3. Mean difference in cough indices (cough diary, cough frequency, cough scores),
4. Proportions experiencing adverse effects of the intervention, (e.g. seizures, school performance etc),
5. Proportions experiencing complications e.g.. requirement for medication change, etc.

It was planned that the proportions of participants who failed to improve on treatment and the mean clinical improvement would be determined using the following hierarchy of assessment measures (i.e. where two or more assessment measures are reported in the same study, the outcome measure that is listed first in the hierarchy will be used).
i) Objective measurements of cough indices (cough frequency, cough receptor sensitivity).

ii) Symptomatic (Quality of life, Likert scale, visual analogue scale, level of interference of cough, cough diary) - assessed by the patient (adult or child)
iii) Symptomatic (Quality of life, Likert scale, visual analogue scale, level of interference of cough, cough diary) - assessed by the parents/carers.
iv) Symptomatic (Likert scale, visual analogue scale, level of interference of cough, cough diary) - assessed by clinicians.
v) Relevant airway markers consistent with inflammation.

Search methods for identification of studies

Electronic searches

The following topic search strategy was used to identify relevant randomised controlled trials in the bibliographic databases:

("cough" OR "bronchitis", all as [textword] or [MeSH]) AND ("theophylline" OR "aminophylline" OR "caffeine" OR "methylxanthines" OR "methylxanthine") AND ("child" OR "children"; all as [textword] or [MeSH])

For the full strategies please see Appendix 1. The latest searches were conducted in October 2010.

Trials were identified from the following sources:

1. The Cochrane Central Register of Controlled Trials (CENTRAL)
2. The Cochrane Airways Group Specialised Register of Trials.
3. MEDLINE (1950 - current). Topic search strategy combined with the RCT search filter as outlined in the Airways Group module.
4. EMBASE (1980 - current). Topic search strategy combined with the RCT search filter as outlined in the Airways Group module.

Searching other resources

5. The list of references in relevant publications.
6. Written communication with the authors of trials included in the review.

Data collection and analysis

Selection of studies

From the title, abstract, or descriptors, all three reviewers independently reviewed literature searches to identify potentially relevant trials for full review. Searches of bibliographies and texts were conducted to identify additional studies. From the full text using specific criteria, the two reviewers (AC, HP) independently selected trials for inclusion. Agreement would have been measured using kappa statistics. It was planned that disagreement be resolved by third party adjudication (RH).

Data extraction and management

Trials that satisfied the inclusion criteria were reviewed and the following information would have been recorded: study setting, year of study, source of funding, patient recruitment details (including number of eligible subjects), inclusion and exclusion criteria, other symptoms, randomisation and allocation concealment method, numbers of participants randomised, blinding (masking) of participants, care providers and outcome assessors, dose and type of intervention, duration of therapy, co-interventions, numbers of patients not followed up, reasons for withdrawals from study protocol (clinical, side-effects, refusal and other), details on side-effects of therapy, and whether intention-to-treat analyses were possible. Data would have been extracted on the outcomes described previously. It was planned that further information be requested from the authors where required.

Assessment of risk of bias in included studies

Studies included in the review would have undergone quality assessment performed independently by two review authors using the 'risk of bias' tool in Revman 5.

Data synthesis

The data would have been analysed as follows. For the dichotomous outcome variables of each individual study, relative and absolute risk reductions calculated using a modified intention-to-treat analysis. This analysis assumes that children not available for outcome assessment have not improved (and probably represents a conservative estimate of effect). An initial qualitative comparison of all the individually analysed studies would have examined whether pooling of results (meta-analysis) was reasonable. This would have taken into account differences in study populations, inclusion/exclusion criteria, interventions, outcome assessment, and estimated effect size.

The results from studies that met the inclusion criteria and reported any of the outcomes of interest would have been included in the subsequent meta-analyses. The summary weighted risk ratio and 95% confidence interval (fixed effects model) would have been calculated using the inverse of the variance of each study result for weighting (Cochrane statistical package, REVMAN version 5). For cross-over studies, mean treatment differences would have been calculated from raw data, extracted or imputed and entered as fixed effects generic inverse variance (GIV) outcome, to provide summary weighted SD unit difference and 95% confidence intervals. In cross-over trials, only data from the first arm would be included in meta analysis if data were combined with parallel studies (Elbourne 2002). Numbers needed to treat (NNT) would have been calculated from the pooled OR and its 95% CI applied to a specified baseline risk using an online calculator (Cates 2003). This calculator converts the risk in the placebo group to the corresponding odds, applies the OR to estimate the odds in the treated group, and converts that odds to the corresponding risk and calculates the risk difference, the inverse of which is the NNT. The cough indices would have been assumed to be normally distributed continuous variables so the mean difference in outcomes can be estimated (weighted mean difference). If studies reported outcomes using different measurement scales, the standardised mean difference would have been estimated. Any heterogeneity between the study results would have been described and tested to see if it reached statistical significance using a chi-squared test. The 95% confidence interval estimated using a random effects model would have been included whenever there are concerns about statistical heterogeneity.

Subgroup analysis and investigation of heterogeneity

An a priori sub-group analysis was planned for children aged less than 7 years and 7 years and above.

Sensitivity analysis

1. Differences in the medications used in the intervention and comparison groups;
2. Differences in outcome measures;
3. Analysis using random effects model;

4. Analysis by "treatment received";
5. Analysis by "intention-to-treat"; and
6. Analysis by study design-parallel and cross over studies

RESULTS

Description of studies

In the original review, the Airways Group specialised register/ search identified 350 potentially relevant titles. After assessing the abstracts, 16 studies were considered for inclusion into review including 3 non-English articles (Polish, German and Spanish). None of the studies fulfilled study criteria. The 2009 and 2010 searches revealed 153 abstracts, of which all were excluded. A pharmaceutical brochure outlining the benefits of a theobromine containing medication (Anycough) for cough was identified during a conference for the 2010 update. The authors wrote to the company but no response was received and no published data could be found.

Risk of bias in included studies

Not applicable.

Effects of interventions

In the absence of appropriate RCTs, four other paediatric papers (Cloutier 1981, Konig 1981, Yahav 1982; Hannaway 1982) that specifically reported on the effect of theophylline on cough in children were also reviewed. All four studies (see excluded table) were non randomised controlled trials and all reported a rapid response, mostly within two to five days and one study (Konig 1981) used theophylline for up to 14 days. One adult study (Cazzola 1993) that was a double blind RCT was also reviewed; in this trial, complete remission in cough was reported in eight of the ten adults after two weeks of oral theophylline. No relevant papers have been identified in update searches.

DISCUSSION

No randomised controlled trials comparing methylxanthines with a placebo in children with non-specific cough were identified. Cohort studies were thus reviewed and while no conclusion about efficacy of theophylline for non specific cough can be made, these studies show that the 'time response' was short i.e. within two days to two weeks. These early studies on the relationship between cough and asthma also show that in many children, other symptoms of asthma (dyspnoea on exertion (Cloutier 1981; Konig 1981), chest pain on exertion (Konig 1981), spirometry abnormalities and/or auscultation abnormalities (Hannaway 1982; Yahav 1982) were present. However some children in these studies had non-specific cough, and did not have clinical features of classical asthma yet all responded to theophylline. However this has to be interpreted in the context of methodological problems in studies with cough as an outcome measure, specifically the large placebo effect, biased subjective reporting, and period effect (Chang 1999).

The pharmacological properties of methylxanthines exceed that of its modest bronchodilator effect (Rabe 1998) and although some of the non-RCT results emphasised its bronchodilator effect, it is unlikely that the rapid response to theophylline was purely related to this effect as the bronchodilator effect of theophylline is only modest.

Given the morbidity associated with chronic cough in children, there is a need for the evaluation of the efficacy of theophylline on non-specific cough in children. Its use however has to be balanced with its associated adverse events as briefly described above (background section).

AUTHORS' CONCLUSIONS

Implications for practice

With the lack of evidence, the routine use of methylxanthines in treating children with non-specific cough cannot be recommended. If methylxanthines were to be trialed in these children, current (but old and limited) cohort data suggest a clinical response (subjective cough severity) usually occurs within two to five days of therapy and definitely within two weeks. However the use of methylxanthines in children with non-specific cough has to be balanced against the well known risk of toxicity and its narrow therapeutic range in children.

Implications for research

Randomised controlled trials of methylxanthines to determine the effectiveness in treating children with non-specific cough are clearly needed. Trials should be parallel studies and double blinded, given the known problems in studying cough, specifically the large placebo and time period effects (Chang 1999). Based on cohort data, a short trial of two weeks would suffice. Outcome measures for the clinical studies on cough should be clearly defined using validated subjective data and supported by objective data when possible.

ACKNOWLEDGEMENTS

We thank Toby Lasserson, Chris Cates, Michael McKean and Emma Welsh from the Airways Group for their advice, supportive role and comments to the protocol and review. We are also very grateful to Elizabeth Arnold for performing the relevant searches and obtaining the articles. We also thank Lech Leskiewicz for translation of German and Polish articles, and Patricia Valery for Spanish translation. Finally we thank Susan Hansen for performing the searches for this update.

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Cloutier 1981 *{published data only}*

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Perez 1994 *{published data only}*

Perez NJ, Serna PC. Functional and clinical evaluation of the bronchodilator effect of acebrophylline in obstructive pulmonary disease in children [Valoracion funcional y clinica del efecfto broncodilatador de la acebrofilina en la patologia pulmonar obstructiva del nino]. *Investigacion Medica Internacional* 1994;**21**(2):67-71.

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Vassallo 1998

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CHARACTERISTICS OF STUDIES

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Bose 1987	Children had clear cut asthma defined as history of recurrent wheeze (> 5 episodes). RCT in children with nocturnal wheeze or cough.
Cazzola 1993	RCT (double blind cross over design) in 10 adults with angiotensin converting enzyme inhibitor induced cough. After 2 weeks of theophylline complete remission was seen in 8 of the 10 adults.
Chyrek 1988	Adult study. Participants had clear cut asthma defined with spirometry change.
Cloutier 1981	Non randomised controlled trial. 15 children with chronic cough treated with theophylline (15-20 mg/kg/day). Cough resolved within 3-5 days in all children.
Hannaway 1982	Non randomised controlled trial. 10 of 32 children had abnormal chest auscultation findings and hence some children in cohort did not have non-specific cough. All responded to theophylline (20-24 mg/kg/day). Authors reproted "dramatic response" in some children.
Konig 1981	Non randomised controlled trial. 6 of the 11 children in this cohort study had dyspnoea on exertion and 2 had chest pain. Thus at least 55% had recognisable clinical asthma. Theophylline (16-20mg/kg/day) and metaproterenol given to all for 1-2 weeks. Authors reported "disappearance of, or great reduction" in cough.
Perez 1994	Cross over RCT that examined the effect of a xanthine (acebrophylline for a week) compared to placebo (one week) using outcomes of cough (in addition to dyspnoea and wheeze). No washout period was described. The entry criteria (asthma and acute bronchitis) was undefined and mean baseline FEV1 was 72%. Thus some children clearly had asthma rather than non-specific cough. The authors reported significantly less cough patient-days in the acebrophylline group (2%) than in the placebo group (5.3%).
Rachelefsky 1980	RCT but clear cut asthma; defined as presence of airway reversibility on spirometry. Study compared metoproterenol to theophylline.
Selby 1997	RCT in adults comparing salbutamol and theophylline. No placebo.
Usmani 2005	RCT in well healthy adults (and animals) and not in adults with chronic cough. Authors assessed effect of theobromine on cough sensitivity .
Yahav 1982	Non randomised controlled trial. 4 of the 15 children had reversibility on spirometry and thus only 11 had non specific cough. 10 children treated with theophylline, 5 with inhaled salbutamol and 2

Study	Reason for exclusion
	received additional corticosteroids. Authors reported that cough cleared in all children within 2-3 days.

APPENDICES

Appendix 1. Database search strategies

1. CENTRAL search

#1 MeSH descriptor Cough explode all trees in MeSH products
#2 MeSH descriptor Bronchitis explode all trees in MeSH products
#3 cough* in All Fields in all products
#4 bronchiti* in All Fields in all products
#5 (#1 OR #2 OR #3 OR #4)
#6 MeSH descriptor Xanthines explode all trees in MeSH products
#7 theophylline* or aminophylline* or caffeine* or methylxanthine* or methyl-xanthine* or xanthine* in All Fields in all products
#8 (#6 OR #7)
#9 (#5 AND #8)

2. MEDLINE search

1. exp COUGH/
2. exp BRONCHITIS/
3. (cough$ or bronchit$).mp.
4. exp XANTHINES/
5. (theophylline$ or aminophylline$ or caffeine$ or methylxanthine$ or methyl-xanthine$ or xanthine$).tw.
6. 1 or 2 or 3
7. 4 or 5
8. 6 and 7
9. ADOLESCENT/ or exp CHILD/ or exp INFANT/
10. exp PEDIATRICS/
11. (child$ or paediat$ or pediat$ or adolesc$ or infan$ or toddler$ or bab$ or young$ or preschool$ or pre school$ or pre-school$ or newborn$ or new born$ or new-born$ or neo-nat$ or neonat$).mp.
12. 9 or 10 or 11
13. 8 and 12

RCT Filter
1. (clinical trial or controlled clinical trial or randomized controlled trial).pt.
2. (randomized or randomised).ab,ti.
3. placebo.ab,ti.
4. dt.fs.
5. randomly.ab,ti.
6. trial.ab,ti.
7. groups.ab,ti.
8. or/1-7
9. Animals/
10. Humans/
11. 9 not (9 and 10)
12. 8 not 11

3. EMBASE search

1. exp COUGHING/
2. exp BRONCHITIS/
3. (cough$ or bronchiti$).tw.
4. 1 or 2 or 3
5. exp Xanthine Derivative/
6. (theophylline$ or aminophylline$ or caffeine$ or methyl-xanthine$ or methylxanthine$ or xanthine$).tw.

7. 5 or 6
8. 4 and 7
9. exp adolescent/ or exp child/ or exp infant/ or exp newborn/
10. (child$ or paediat$ or pediat$ or adolesc$ or infan$ or toddler$ or bab$ or young$ or preschool$ or pre school$ or pre-school$ or newborn$ or new born$ or new-born$ or neo-nat$ or neonat$).tw.
11. exp PEDIATRICS/
12. 9 or 10 or 11
13. 8 and 12

RCT Filter

1. Randomized Controlled Trial/
2. Controlled Study/
3. randomization/
4. Double Blind Procedure/
5. Single Blind Procedure/
6. Clinical Trial/
7. Crossover Procedure/
8. follow up/
9. exp prospective study/
10. or/1-9
11. (clinica$ adj3 trial$).mp.
12. ((singl$ or doubl$ or trebl$ or tripl$) adj5 (mask$ or blind$ or method$)).mp.
13. exp Placebo/
14. placebo$.mp.
15. random$.mp.
16. (latin adj3 square$).mp.
17. exp Comparative Study/
18. ((control$ or prospectiv$ or volunteer$) adj3 (trial$ or method$ or stud$)).mp.
19. (crossover$ or cross-over$).mp.
20. or/11-19
21. 10 or 20
22. exp ANIMAL/
23. Nonhuman/
24. Human/
25. 22 or 23
26. 25 not 24
27. 21 not 26

4. Airways Register search

(#45=COUGH//) and (theophylline* or aminophylline* or caffeine* or methylxanthine* or methyl-xanthine* or xanthine*)

WHAT'S NEW

Date	Event	Description
14 October 2010	New search has been performed	New literature search. No new studies were included.

HISTORY

Protocol first published: Issue 2, 2005
Review first published: Issue 3, 2005

Date	Event	Description
24 March 2009	Amended	Change of contact details

Date	Event	Description
14 January 2009	New search has been performed	Literature search re-run; no new studies identified.
7 August 2008	Amended	Converted to new review format.
22 February 2005	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

AC: initiation, formulation and writing of protocol. HP and RH: writing of protocol. For the review- AC: review and selection of studies from search, data extraction and writing of review. HP: review and selection of studies from search, and writing of review. RH: selection of studies from search and writing of review.

DECLARATIONS OF INTEREST

None known.

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- Royal Children's Hospital Foundation, Australia.

External sources

- National Health and Medical Research Council, Australia.

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INDEX TERMS

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MeSH check words

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