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

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[Intervention Review]

Anticholinergics 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 inhaled anti-cholinergic medications.

Objectives

To determine the efficacy of inhaled anti-cholinergic medications in the management of prolonged non-specific cough in children.

Search methods

The Cochrane Register of Controlled Trials (CENTRAL), MEDLINE and EMBASE databases were searched. Relevant pharmaceutical companies were contacted. The latest searches were carried out in April 2010.

Selection criteria

All randomised controlled trials comparing inhaled anti-cholinergic medication with a placebo medication.

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. A single small trial in adults has been reported.

Main results

No randomised-controlled trials that examined the efficacy of inhaled anti-cholinergic medications in the management of prolonged non-specific cough in children were found. An additional search in April 2010 did not identify any further studies.

Authors' conclusions

There is currently no evidence to support the use of inhaled anti-cholinergics for symptomatic control of non-specific cough in children. Further research examining the effects of this intervention is needed.

PLAIN LANGUAGE SUMMARY

Anticholinergics for prolonged non specific cough in children

Children with non-specific cough, (non-productive cough in the absence of identifiable chest disease) are commonly treated with a variety of medications for control of cough symptoms. This review examined the effect of inhaled anti-cholinergic drugs in children with non-specific cough. Currently there is no evidence to support the use of inhaled anti-cholinergics as no randomised-controlled trials of inhaled anti-cholinergic medications in the management of prolonged non-specific cough in children were found.

BACKGROUND

Cough is a very common symptom of respiratory disease and the commonest symptom for presentation to family doctors [Britt 2002]. The definition of chronic cough in children varies from longer than 3 weeks to longer than 6 weeks. Prevalence ranges from 3% in Dutch school children [Spee-van 1998] to 35% in South African children [Nriagu 1999]. However, the reporting of isolated cough in questionnaires is however unreliable [Brunekreef 1992] and prevalence figures are probably inaccurate.

Non-specific cough is defined as non-productive cough in the absence of identifiable respiratory disease or known aetiology [Chang 2001]. Children with a history of nonspecific cough are commonly seen in paediatric practice. The majority have no signs of other current disease processes. In the absence of research to guide clinical practice, these children are treated with a variety of therapies: antibiotics, cough suppressants, anti-histamines, decongestants, bronchodilators, anticholinergics, sodium cromoglycate, inhaled corticosteroids and oral corticosteroids. These interventions sometimes result in significant side effects [Thomson 2002].

Children with non-specific cough present a major management problem and cause considerable anxiety to parents. The desire by patients and medical practitioners to treat cough is reflected in the wide use of over-the-counter (OTC) medications for coughs and the frequent prescription of antibiotics for upper respiratory tract infection [McManus 1997]. Many children with non-specific cough are treated with asthma type medications (corticosteroids and/or bronchodilators). However, beneficial effects of these interventions have not been clearly described.

A Cochrane Review on the use of beta2-agonists for acute bronchitis focused on acute cough (undefined time frame) in adults and children. The reviewers concluded that use of beta2-agonists confers no benefit in the absence of airflow obstruction [Smucny 2006]. This present review focuses on prolonged non-specific cough in children. This condition is most likely to differ from acute bronchitis with respect to the duration of cough (>3 weeks) and the quality of cough (non-productive).

OBJECTIVES

To determine the efficacy of inhaled anti-cholinergic medications in treating children with non-specific cough.

METHODS

Criteria for considering studies for this review

Types of studies

All randomised controlled trials comparing inhaled anti-cholinergic medications with a placebo medication.

Types of participants

All trials which included children under 18 years of age with prolonged (3 or more weeks) non-specific cough (dry and non-productive cough without any other respiratory symptom, sign or systemic illness). An a priori subgroup analysis was planned for children aged < 7 years.

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 anti-cholinergic medications versus placebo medication in the management of non-specific cough. Trials only comparing two or more asthma medications without a placebo comparison group were not included. Two separate treatment regimes were evaluated:

1. Inhaled anticholinergic medications by metered dose inhaler (with or without spacer device),
2. Inhaled anticholinergic medications by nebuliser

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

Attempts were made to obtain data on at least one of the following outcome measures:

Primary outcomes

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

Secondary outcomes

b) proportions of participants who were not cured at follow up,
c) proportions of participants who not substantially improved at follow up,
d) mean difference in cough indices (cough diary, cough frequency, cough scores),
e) proportions experiencing adverse effects, e.g.. tremor, behavioral changes (side effects),
f) proportions experiencing complications e.g.. requirement for medication change.
g) proportions of participants expressing preference for medication or placebo.
h) proportions of parent/carers expressing preference for medication or placebo.

The proportions of participants who failed to improve on treatment and the mean clinical improvement were 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 was listed first in the hierarchy was used).

1. Objective measurements of cough indices (cough frequency, cough receptor sensitivity, cough amplitude).
2. Symptomatic (Likert scale, visual analogue scale, level of interference of cough, cough diary) - assessed by the child.
3. Symptomatic (Likert scale, visual analogue scale, level of interference of cough, cough diary) - assessed by the parents/carers.
4. Symptomatic (Likert scale, visual analogue scale, level of interference of cough, cough diary) - assessed by clinicians.
5. Airway markers consistent with infection or inflammation.

Search methods for identification of studies

The following topic search strategy was used to identify relevant randomised controlled trials:
(cough [MeSH] OR cough [text word] OR bronchitis [MeSH] OR bronchitis [text word]) AND (bronchodilator [MeSH] OR bronchodilator [text word] or anti cholinergic [MeSH] OR anticholinergic [text word] OR ipratropium [text word] OR ipratropium bromide [text word]). The full strategies are listed in Appendix 1. The latest searches were carried out in April 2010.
Trials were identified from the following sources:

1. The Cochrane Register of Controlled Trials (CENTRAL) (which includes the Airways Collaborative Review Group Specialised Trials Register).
2. MEDLINE 1966-current. Topic search strategy combined with the MEDLINE randomised controlled trial search filter as outlined in the Airways Group module.
3. OLDMEDLINE 1950-1965. Topic search strategy combined with the MEDLINE randomised controlled trial search filter as outlined in the Airways Group module.
4. EMBASE 1980-current. Topic search strategy combined with the EMBASE randomised controlled trial search filter as outlined in the Airways Group module.
5. Reference lists in relevant publications.
6. Written communication with the authors of trials included in the review.
7. Written communication with major pharmaceutical companies (with offices in Australia) that manufacture anticholinergic medications.

Data collection and analysis

Retrieval of studies: Abstracts of papers identified from the search were read by both reviewers (ABC, PM) who then independently reviewed potentially relevant trials for full review. Searches of bibliographies and texts were conducted to identify additional studies. In addition ABC wrote to manufacturers of ipratropium with links in Australia. It was planned that agreement would be measured

using kappa statistics and disagreement resolved by consensus or third party adjudication (M McKean).

Planned data analysis:

Trials that satisfied the inclusion criteria would have been reviewed and the following information recorded: study setting, year of study, source of funding, patient recruitment details (including number of eligible children), inclusion and exclusion criteria, randomisation and allocation concealment method, numbers of participants randomised, blinding (masking) of participants, care providers and outcome assessors, dose and type of anti-cholinergic therapy, 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. Further information would have been requested from the authors where required.

Studies included in the review would have undergone quality assessment performed independently by all reviewers. Four components of quality would have been assessed:

1. Allocation concealment. Trials scored as: Grade A: Adequate concealment, Grade B: Unclear, Grade C: Clearly inadequate concealment. (Grade A = high quality).
2. Blinding. Trials scored as: Grade A: Participant and care provider and outcome assessor blinded, Grade B: Outcome assessor blinded, Grade C: Unclear, Grade D: No blinding of outcome assessor (Grade A, B = high quality).
3. Reporting of participants by allocated group. Trials scored as: Grade A: The progress of all randomised children in each group described, Grade B: Unclear or no mention of withdrawals or dropouts, Grade C: The progress of all randomised children in each group clearly not described. (Grade A = high quality).
4. Follow-up. Trial scored as: Grade A: Outcomes measured in >90% (where withdrawals due to complications and side-effects are categorised as treatment failures), Grade B: Outcomes measured in 80-90%, Grade C: Unclear, Grade D: Outcomes measured in <80%. (Grade A = high quality).

While only the allocation concealment quality assessment would have been displayed in the meta-analysis figures, all assessments would have been included in the "Characteristics of included studies" table. Inter-reviewer reliability for the identification of high quality studies for each component would have been measured by the Kappa statistic.

For the dichotomous outcome variables of each individual study, relative and absolute risk reductions would have been 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 take 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) were to be calculated using the inverse of the variance of each study result for weighting (Cochrane statistical package, REVMAN version 5). The number needed to treat was to be calculated using the summary odds ratio and the average control event rate described in the relevant studies. The cough indices were to be 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 was to be estimated. Any heterogeneity between the study results was to be described and tested to see if it reached statistical significance using a chi-squared test (where $p< 0.1$ is considered significant). The 95% confidence interval estimated using a random effects model was to be included whenever there are concerns about statistical heterogeneity.

An a priori sub-group analysis was planned for children less than 7 years of age. Sensitivity analyses were planned to assess the impact of the potentially important factors on the overall outcomes: a) study quality; b) study size; c) variation in the inclusion criteria; d) differences in the medications used in the intervention and comparison groups; e) differences in outcome measures; f) analysis by standard intention-to-treat (children not available for outcome assessment not included) rather than modified intention-to-treat, and g) analysis by "treatment received (children not available for outcome assessment and children who did not receive intervention in accordance with protocol not included) rather than modified "intention-to-treat".

RESULTS

Description of studies

See: Characteristics of excluded studies.

The searches identified 4 potential studies but all did none fulfilled the study eligibility criteria.

Risk of bias in included studies

Not applicable

Effects of interventions

The Airways Group specialised register/search identified 864 potentially relevant titles. After assessing the abstracts, only 4 studies were considered for inclusion into review. Three other studies

were further identified from the additional sources. None of the studies fulfilled study criteria. One study did evaluate the effectiveness of an inhaled anti-cholinergic medication in prolonged non-specific cough but only included adults [Holmes 1992]. Additional searches in subsequent years (April 2004, 2005, 2006, 2007, 2008, 2009 and 2010) did not identify any further studies. One study that used nasal ipratropium (for 'colds') was excluded as it did not meet the inclusion criteria of the review.

DISCUSSION

No randomised controlled trials of inhaled anti-cholinergic medications for the treatment of persistent non-specific cough in children were identified. A small randomised, double blind, crossover trial involving 14 adults with persistent cough following a viral infection has been conducted [Holmes 1992]. The investigators reported an overall clinical improvement and reduction in cough scores in the participants while they were receiving ipratropium bromide (4 puffs of 20 micrograms, four times daily).

At this point, routine use of inhaled anti-cholinergic medications cannot be recommended for children. Parents requesting a trial of therapy should be informed of the lack of any well-designed studies assessing effectiveness, the associated cost of treatment, and the risk of side-effects. The manufacturer of first inhaled anti-cholinergic medications indicated that none of their anti-cholinergic medications are indicated for treatment of cough in children.

AUTHORS' CONCLUSIONS

Implications for practice

There is currently no evidence to support the use of inhaled anti-cholinergics in children with non specific cough. The known adverse events (e.g. paradoxical bronchospasm, paralytic ileus, tachycardia) must also be considered if inhaled cholinergics medications are used.

Implications for research

Randomised controlled studies to determine the effectiveness of inhaled anti-cholinergic medications for symptomatic control of cough in children with non specific cough are needed.

ACKNOWLEDGEMENTS

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REFERENCES

References to studies excluded from this review

Dicpinigaitis 2008 *{published data only}*
Dicpinigaitis PV, Spinner L, Santhyadka G, Negassa A. Effect of tiotropium on cough reflex sensitivity in acute viral cough. *Lung* 2008;**186**:369–74.

Graf 2009 *{published data only}*
Graf P, Eccles R, Chen S. Efficacy and safety of intranasal xylometazoline and ipratropium in patients with common cold. *Expert Opinion on Pharmacotherapy* 2009;**10**: 889–908.

Holmes 1992 *{published data only}*
Holmes PW, Barter CE, Pierce RJ. Chronic persistent cough: use of ipratropium bromide in undiagnosed cases following upper respiratory tract infection. *Respiratory Medicine* 1992;**86**(5):425–9.

Lowry 1994 *{published data only}*
Lowry R, Wood A, Higenbottam T. The effect of anticholinergic bronchodilator therapy on cough during upper respiratory tract infections. *British Journal of Clinical Pharmacology* 1994;**37**(2):187–91.

Pulejo 1986 *{published data only}*
Pulejo R, Romano L, Noto M. Double-blind study with Duovent and placebo in 20 asthmatic children. *Respiration* 1986;**50**(Suppl 2):236–239.

Shore 1981 *{published data only}*
Shore SC, Weinberg EG. Ipratropium bromide inhalation for allergic rhinitis and chronic cough. *South African Medical Journal* 1981;**59**(8):252.

Additional references

Britt 2002
Britt H, Miller GC, Knox S, Charles J, Valenti L, Henderson J, et al.*Bettering the Evaluation and Care of Health - A Study of General Practice Activity (AIHW Cat. No. GEP-10).* Australian Institue of Health and Welfare, 2002.

Brunekreef 1992
Brunekreef B, Groot B, Rijcken B, Hoek G, Steenbekkers A, de Boer A. Reproducibility of childhood respiratory symptom questions. *European Respiratory Journal* 1992;**5** (8):930–5.

Chang 2001
Chang AB, Asher MI. A review of cough in children. *Journal of Asthma* 2001;**38**(4):299–309.

McManus 1997

McManus P, Hammond ML, Whicker SD, Primrose JG, Mant A, Fairall SR. Antibiotic use in the Australian community, 1990-1995. *Medical Journal of Australia* 1997; **167**(3):124–7.

Nriagu 1999

Nriagu J, Robins T, Gary L, Liggans G, Davila R, Supuwood K, et al.Prevalence of asthma and respiratory symptoms in south-central Durban, South Africa. *European Journal of Epidemiology* 1999;**15**(8):747–55.

Smucny 2006

Smucny J, Flynn C, Becker L, Glazier R. Beta2-agonists for acute bronchitis (Cochrane Review). *Cochrane Database of Systematic Reviews* 2006, Issue 4. [DOI: 10.1002/14651858.CD001726.pub3.]

Spee-van 1998

Spee-van der Wekke J, Meulmeester JF, Radder JJ, Verloove-Vanhorick SP. School absence and treatment in school children with respiratory symptoms in The Netherlands: data from the Child Health Monitoring System. *Journal of Epidemiology and Community Health* 1998;**52**(6):359–63.

Thomson 2002

Thomson F, Masters IB, Chang AB. Persistent cough in children - overuse of medications. *Journal of Paediatrics and Child Health* 2002;**38**(6):578–81.

* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Study	Reason for exclusion
Dicpinigaitis 2008	Study in adults with acute cough associated with a viral infection
Graf 2009	This review assesses two widely used intranasal treatments for nasal congestion and rhinorrhea in the common cold: xylometazoline hydrochloride and ipratropium bromide. Thus does not fit into criteria of non-specific chronic cough
Holmes 1992	Study on 14 adults with post viral infective cough
Lowry 1994	Study on 56 adults with cough associated with cold
Pulejo 1986	Cough associated with classical asthma and thus does not fit into criteria of non-specific chronic cough
Shore 1981	Non randomised report

DATA AND ANALYSES

This review has no analyses.

APPENDICES

Appendix 1. Database Search Strategies

CENTRAL

#1 COUGH
#2 BRONCHITIS
#3 cough*
#4 bronchit*
(#1 or #2 or #3 or #4)
#5 CHOLINERGIC ANTAGONISTS
#6 (anticholinergic* or anti-cholinergic*)
#7 ipratropium
#8 (cholinergic* near antagonist*)
#9 (cholinergic* near block*)
#10 (acetylcholine or cholinolytic*)
#11 (atrovent or aerocap* or aerohaler* or autohaler* or respontin or tropiovent)
#12 (#6 or #7 or #8 or #9 or #10 or #11 or #12)
#13 (#5 and #13)

MEDLINE

1. exp Cough/
2. exp Bronchitis/
3. cough$.mp.
4. bronchit$.mp.
5. 1 or 2 or 3 or 4
6. exp Cholinergic Antagonists/
7. (anticholinergic$ or anti-cholinergic$).mp.
8. Ipratropium.mp.
9. (cholinergic$ adj3 antagonist$).mp.
10. (cholinergic$ adj3 block$).mp.
11. (acetylcholine or cholinolytic$).mp.
12. (Atrovent or Aerocap$ or Aerohaler$ or Autohaler$ or Respontin or Tropiovent).mp.
13. 6 or 7 or 8 or 9 or 10 or 11 or 12
14. 5 and 13

EMBASE

1. exp Coughing/
2. cough$.mp.
3. exp BRONCHITIS/
4. bronchit$.mp.
5. 1 or 2 or 3 or 4

6. exp Cholinergic Receptor Blocking Agent/
7. (anticholinergic$ or anti-cholinergic$).mp.
8. exp Ipratropium Bromide/
9. (cholinergic$ adj3 antagonist$).mp.
10. (cholinergic$ adj3 block$).mp.
11. (acetylcholine or cholinolytic$).mp.
12. (Ipratropium or Atrovent or Aerocap$ or Aerohaler$ or Autohaler$ or Respontin or Tropiovent).mp.
13. 6 or 7 or 8 or 9 or 10 or 11 or 12
14. 5 and 13

WHAT'S NEW

Last assessed as up-to-date: 13 April 2010.

Date	Event	Description
14 April 2010	New search has been performed	New search. No new studies found
26 January 2010	Amended	Reporting of search dates in abstract corrected.

HISTORY

Protocol first published: Issue 1, 2003

Review first published: Issue 4, 2003

Date	Event	Description
10 May 2009	New search has been performed	New search - no relevant studies found
24 March 2009	Amended	Change of contact details
5 April 2008	Amended	Converted to new review format.
1 April 2008	Amended	Search re-run; no new trials eligible for inclusion in the review
21 July 2003	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

ABC and PM wrote the protocol, review and independently reviewed potential abstracts and papers. MM contributed to final protocol and review

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- Royal Children's Hospital Foundation, Brisbane, Australia.
- National Health and Medical Research Council, Australia.

External sources

- No sources of support supplied

INDEX TERMS

Medical Subject Headings (MeSH)

Administration, Inhalation; Cholinergic Antagonists [*therapeutic use]; Cough [*drug therapy]

MeSH check words

Child; Humans