Acetylcysteine and carbocysteine for acute respiratory tract infections in paediatric patients without chronic bronchopulmonary disease (Protocol)

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ABSTRACT
This is the protocol for a review and there is no abstract. The objectives are as follows:
1. To assess the efficacy of the use of acetylcysteine and carbocysteine as symptomatic treatment for acute respiratory tract infections in paediatric patients without chronic bronchopulmonary disease.
2. To evaluate the safety of the use of acetylcysteine and carbocysteine as symptomatic treatment for acute respiratory tract infections in paediatric patients without chronic bronchopulmonary disease.
3. To establish the benefit-risk ratio of the use of acetylcysteine and carbocysteine as symptomatic treatment for acute respiratory tract infections in paediatric patients without chronic bronchopulmonary disease.

BACKGROUND
Among mucolytic agents, cysteine derivates (i.e. acetylcysteine and carbocysteine) are the most commonly prescribed drugs (Duijvestijn 1997; Chalumeau 2000). In vitro, they break disulphide bridges between macromolecules and lead to a reduction of mucus viscosity (Medici 1979).

Because of this property, the development of these drugs was conducted in the 60’s and 70’s in clinical situations where sputum reduction was sought: cystic fibrosis, and chronic and acute bronchitis. In adult patients, the use of cysteine derivates is associated with a small reduction in acute exacerbations of chronic bronchitis (Poole 2000) and may help sputum production in bronchiectasis (Crockett 2000). In paediatric patients with cystic fibrosis, there is no evidence of effectiveness of either oral or inhaled administration of acetylcysteine (Duijvestijn 1999).

In some countries, in addition to being used for patients with severe chronic underlying pulmonary disease, cysteine derivates are also widely used in previously healthy paediatric patients with acute respiratory tract infections. In the Netherlands, one third of general practitioners prescribe acetylcysteine for asthmatic bronchitis, acute bronchitis, or for productive or dry cough (Duijvestijn 1997). In France, it has been reported that acetylcysteine and carbocysteine represent 4% of the total amount of drug prescriptions by office-based paediatricians (Chalumeau 2000). In the same study, cysteine derivates accounted for 18-25% of drug prescriptions for acute rhinopharyngitis, acute cough and acute bronchitis. In the United States, the use of acetylcysteine for the treatment of respiratory tract infections in paediatric patients is considered effective with good documentation in the widely used drug data base Micromedex.

To our knowledge, there is no published systematic review of the effectiveness and safety associated with the use of acetylcysteine and carbocysteine for acute respiratory tract infections in paediatric patients without chronic bronchopulmonary disease.

OBJECTIVES
1. To assess the efficacy of the use of acetylcysteine and carbocysteine as symptomatic treatment for acute respiratory tract infec-
2. To evaluate the safety of the use of acetylcysteine and carbocysteine as symptomatic treatment for acute respiratory tract infections in paediatric patients without chronic bronchopulmonary disease.

3. To establish the benefit-risk ratio of the use of acetylcysteine and carbocysteine as symptomatic treatment for acute respiratory tract infections in paediatric patients without chronic bronchopulmonary disease.

CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW

Types of studies

Randomised controlled trials comparing the systemic or inhaled use of acetylcysteine and carbocysteine versus placebo either alone or as an add-on therapy (see types of interventions).

Types of participants

Trials will be included regardless of patient sex and study setting (ambulatory or hospital based).

Trials will be included if the patients meet all of the following criteria:

- age less than 18 years;
- physician's diagnosis of respiratory tract infection, acute pneumonia, acute bronchitis, acute bronchiolitis (secondary to respiratory syncytial virus or to other virus) or acute cough (including pertussis);
- duration of symptoms less than 4 weeks.

Trials on patients with any of the following conditions will be excluded:

- acetaminophen (paracetamol) intoxication;
- bronchiectasis, cystic fibrosis or bronchopulmonary dysplasia;
- underlying immunodeficiency or respiratory tract anatomical defect;
- acute respiratory distress requiring mechanical ventilation.

Trials on patients with underlying asthma or tuberculosis (as defined by the investigators) will be included.

Types of intervention

Trials on the systemic use (i.e. oral, intramuscular or intravenous uses) or inhaled use of acetylcysteine or carbocysteine will be included regardless of the dose regimen used.

Trials which allowed concurrent use of other treatments (such as antibiotics, corticosteroids, bronchodilators, antitussives, chest physiotherapy, analgesics, or antipyretics) will be included if they allowed equal access to such medications for patients in the intervention and control groups.

Types of outcome measures

Trials comparing the use of acetylcysteine or carbocysteine in association with other medications (such as antibiotics, corticosteroids, bronchodilators, antitussives, chest physiotherapy, analgesics, or antipyretics) versus placebo will be used to study the safety of the use of acetylcysteine or carbocysteine in association with other treatments.

Types of outcome measures

- time to resolution of clinical symptoms (such as increased respiratory rate, use of accessory respiratory muscles, abnormal lung examination, cough, sputum production, fever, or activity limitations);
- proportions of patients with clinical symptoms at a designated time;
- global assessment of improvement by clinicians, patients or their parents at follow-up (or at another designated time);
- decreased hospitalisation rates and/or duration of hospitalisation;
- adverse events reported by the investigators.

SEARCH METHODS FOR IDENTIFICATION OF STUDIES

See: methods used in reviews.

Published trials

Electronic searches for relevant studies will be performed by at least one of the three first authors in the following data bases: Cochrane Acute Respiratory Infections Group's Trial Register, Cochrane Controlled Trials Register, EMBASE, MEDLINE, Micromedex, Pascal and Science Citation Index. The following MeSH terms will be used for the search: acetylcysteine, carbocysteine, expectorants. Mucolytics will be used as a text word.

The references of relevant trials will be used to identify other trials.

Unpublished trials

We will request information of unpublished trials from:

- drug companies that manufacture acetylcysteine or carbocysteine in France, Netherlands and the United States;
- authors of relevant published articles.

The results of each step of the electronic search and the lists of drug companies and authors contacted will be described.

Language restrictions

None.
METHODS OF THE REVIEW

The first three authors will use titles and abstracts to select potentially relevant articles. Full text for these articles will be obtained. Full text for ambiguous titles or abstracts will also be obtained.

The same authors will independently select articles felt to be relevant for the analysis. At this step, discrepancies between the first three authors will be resolved by the remaining two authors.

Three investigators will independently grade the quality of each included study using the Jadad scale. Points will be given for method of randomization [0-2], adequacy of blinding [0-2], and handling of withdrawals [0-1], for a total of 0-5 for each study (Jadad 1996). Agreement on quality will be assessed with a kappa score, and disagreements resolved by discussion and consensus.

The same three investigators will then independently extract the data from each study. Again, any disagreements will be resolved by discussion and consensus. We will attempt to contact trial authors to obtain any missing data.

Summary statistics will be calculated on RevMan 4.1. We will use fixed effects models for outcomes without statistically significant heterogeneity (at p < 0.10) and random effects models for outcomes with significant heterogeneity. For dichotomous outcomes (such as the presence or absence of a symptom at the time of follow-up), we will report relative risks, absolute risk differences, and numbers needed to treat or harm. In calculating relative risks, RevMan 4.1 adds 0.5 to cells with zero values. For continuous linear outcomes (such as duration of symptoms in days), we will report weighted mean differences; and for continuous ordinal outcomes (such as cough symptom scores), standardized mean differences. We will consider a level of p < 0.05 as being statistically significant.

A sensitivity analysis on the route of administration and the dosages of acetylcysteine and carbocysteine will be performed if necessary. If studies differ considerably by quality, a sensitivity analysis that excludes the low quality studies (total quality scores <2) will be performed.

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POTENTIAL CONFLICT OF INTEREST

No financial conflict of interest.

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REFERENCES

Additional references
Chalumeau 2000

Crockett 2000

Duijvestijn 1997

Duijvestijn 1999

Jadad 1996
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