

Oral mucolytic drugs for exacerbations of chronic obstructive pulmonary disease: systematic review

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Abstract

Objective To assess the effects of oral mucolytics in adults with stable chronic bronchitis and chronic obstructive pulmonary disease.

Design Systematic review of randomised controlled trials that compared at least two months of regular oral mucolytic drugs with placebo.

Studies Twenty three randomised controlled trials in outpatients in Europe and United States.

Main outcome measures Exacerbations, days of illness, lung function, adverse events.

Results Compared with placebo, the number of exacerbations was significantly reduced in subjects taking oral mucolytics (weighted mean difference -0.07 per month, 95% confidence interval -0.08 to -0.05 , $P < 0.0001$). Based on the annualised rate of exacerbations in the control subjects of 2.7 a year, this is a 29% reduction. The number needed to treat for one subject to have no exacerbation in the study period would be 6. Days of illness also fell (weighted mean difference -0.56 , -0.77 to -0.35 , $P < 0.0001$). The number of subjects who had no exacerbations in the study period was greater in the mucolytic group (odds ratio 2.22, 95% confidence interval 1.93 to 2.54, $P < 0.0001$). There was no difference in lung function or in adverse events reported between treatments.

Conclusions In chronic bronchitis and chronic obstructive pulmonary disease, treatment with mucolytics is associated with a reduction in acute exacerbations and days of illness. As these drugs have to be taken long term, they could be most useful in patients who have repeated, prolonged, or severe exacerbations of chronic obstructive pulmonary disease.

Introduction

At least half of smokers will develop chronic bronchitis,¹ and up to 15% will develop limiting symptoms from chronic obstructive pulmonary disease.² People with chronic bronchitis or chronic obstructive pulmonary disease may experience recurrent exacerbations with worsening symptoms or greater volume or purulence of sputum. These exacerbations contribute to morbidity and poorer health³ as well as to increased healthcare costs.⁴

Although these exacerbations can be treated with antibiotics or steroids, it would be useful to have other

treatments that reduced the frequency and duration of acute exacerbations. Mucolytics increase the expectoration of sputum by reducing its viscosity or hypersecretion.⁵ Some are also antioxidants.⁶ These drugs might be of benefit in reducing exacerbations of chronic obstructive pulmonary disease. In some European countries, mucolytics are widely prescribed in the belief that they reduce the frequency of exacerbations or symptoms in patients with chronic bronchitis. However, in the United Kingdom and Australasia, mucolytics are used infrequently because they are perceived to be ineffective. Two oral mucolytics are currently available in the United Kingdom (carbocysteine and mecysteine)⁷ and one in New Zealand (bromhexine). These drugs, however, are not funded in either country for adults with chronic obstructive pulmonary disease.

We conducted a systematic review to determine, firstly, if treatment with mucolytics reduced the frequency of exacerbations or days of illness in people with chronic bronchitis or chronic obstructive pulmonary disease and, secondly, to determine if mucolytics improve lung function or increase adverse events.

Methods

We did the first Cochrane systematic review on this topic in 1997 and updated it in 1999 using similar methods.⁸ We identified abstracts using the Cochrane Airways Group register. We searched the register using the following terms: (chronic bronchitis or chronic obstructive pulmonary disease) and (mucolytics or *N*-acetylcysteine or bromhexine or *S*-carboxymethylcysteine or ambroxol or sobrerol or iodinated glycerol). Further details of the search strategy are available on the *BMJ*'s website.

The included studies were randomised, double blind, placebo controlled studies of oral mucolytics taken regularly for at least two months. We excluded trials of inhaled mucolytics; combinations of mucolytics with antibiotics or bronchodilators; deoxyribonucleases; and proteases such as trypsin. Participants were adults (>20 years) with chronic bronchitis or chronic obstructive pulmonary disease defined according to Medical Research Council, European Respiratory Society, or American or British Thoracic Society guidelines. Studies on people with asthma or cystic fibrosis were excluded.

The primary outcome measures were the number of acute exacerbations (including the number of

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BMJ 2001;322:1271-4

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participants with no exacerbations in the study period) and days of illness (defined as days in bed, days off work, or days when the participant was unable to undertake normal activities). Days taking antibiotics were also assessed. The secondary outcome measures were measures of lung function (including forced expiratory volume in one second, forced vital capacity, and peak expiratory flow rate) and adverse effects of treatment.

Results

Twenty seven trials studied double blind placebo controlled treatment with an oral mucolytic drug for at least eight weeks. Four of these were excluded because they did not provide information on the primary outcome.⁹⁻¹² The remaining 23 studies are included in the review (R Meister, long term treatment with acetylcysteine retard, 1986).¹³⁻³⁴ Twenty one studied people with chronic bronchitis and two studied people with chronic obstructive pulmonary disease. Details of these studies are available on the *BMJ's* website.

Exacerbations

Regular use of mucolytics was associated with a reduction of 0.07 exacerbations per patient a month (95% confidence interval -0.08 to -0.05, $P < 0.0001$, fig). The odds ratio for having no exacerbation in the study period with mucolytic treatment compared with placebo was 2.22 (95% confidence interval 1.93 to 2.54, $P < 0.0001$). Based on these numbers, the number needed to treat for one subject to remain free of exacerbations for the study period would be 6. In contrast to the results seen for other drugs, there was no significant reduction in exacerbation rates with the thiol donor, isobutylcysteine.²²

Days of illness

Mucolytic therapy significantly reduced the number of days of illness per subject per month by 0.56 days (95% confidence interval -0.77 to -0.35, $P < 0.0001$). Simi-

larly, the number of days that subjects took antibiotics was reduced by 0.53 a month (-0.76 to -0.31, $P < 0.0001$).

Lung function

In the few studies that reported this outcome, the differences in both forced expiratory volume in one second and forced vital capacity between subjects receiving mucolytic drugs and placebo were small and not significant.

Adverse events

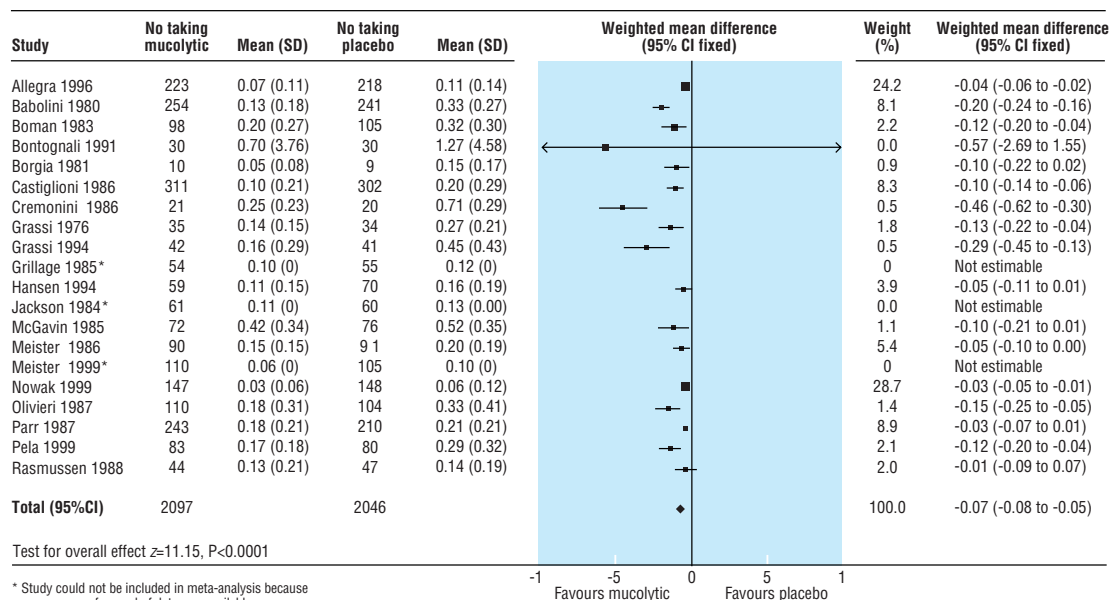
Adverse events were usually mild and self limiting. There were 1890 adverse events in 2450 subjects taking mucolytic drugs and 1882 events in 2453 subjects taking placebo (mean of 0.77 events per subject in both groups).

Discussion

Our systematic review shows that mucolytic drugs have a modest but significant effect on exacerbation rates in people with chronic bronchitis and chronic obstructive pulmonary disease. The reduction of 0.07 exacerbations per month is 29% lower than the rate in the control group. On the basis of the annualised exacerbation rate (weighted for study size) of 2.7 per patient per year in the control group, mucolytic treatment was associated with a reduction of 0.79 exacerbations per patient per year. This approach, however, tends to overestimate the annual number of exacerbations as more exacerbations occur during winter, when most of these studies were done.

Is treatment justified?

Clinicians and patients will need to judge for themselves whether the reductions in exacerbation rate and days of illness seen with mucolytic drugs are large enough to warrant daily treatment for at least three to six months a year. At recommended doses, the available mucolytics in United Kingdom cost over



Mean (SD) number of exacerbations per subject per month, weighted mean difference, and 95% confidence intervals

What is already known on this topic

Mucolytic drugs have properties that may be beneficial in chronic obstructive pulmonary disease

These drugs are not prescribed in the United Kingdom and Australasia, although they are widely used in many other countries

Drugs that reduce exacerbations may reduce the morbidity and healthcare costs associated with progressively severe disease

What this study adds

Regular use of mucolytic drugs for at least two months significantly reduces exacerbations and days of illness compared with placebo in patients with chronic bronchitis and chronic obstructive pulmonary disease

Exacerbations that do occur may not be as severe, and the benefit may be greater in those with more severe disease

Reductions are modest and treatment may not be cost effective

£200 a year. A short course of amoxicillin or prednisolone for one infective exacerbation costs around £2.⁷ In most of the studies, subjects had mild chronic obstructive pulmonary disease, defined by their degree of airways obstruction. A recent analysis of the cost effectiveness of acetylcysteine in chronic bronchitis suggested that the point at which the costs of treatment and non-treatment are equal was 0.6 fewer exacerbations per six months.³⁵ In our review, exacerbations decreased by less than this (0.4 per six months). However, evidence from the two studies in patients with a mean forced expiratory volume less than 50% of predicted showed a reduction in the exacerbation rate of 0.13 per patient per month (0.8 per six months), suggesting that the benefit may be greater in those with more severe chronic obstructive pulmonary disease. Patients who have frequent or prolonged exacerbations or those who are repeatedly admitted to hospital with exacerbations of chronic obstructive pulmonary disease may also benefit more.

Future randomised controlled trials should examine the value of mucolytic drugs in patients who have repeated, prolonged, or severe exacerbations or who are repeatedly admitted to hospital with exacerbations of chronic obstructive pulmonary disease. None of the studies in this review reported the effect of treatment with mucolytics on hospital admission for chronic obstructive pulmonary disease. It is important that this outcome is included in future studies as it contributes greatly to the costs of treating severe chronic obstructive pulmonary disease. Use of mucolytics in acute exacerbations of chronic obstructive pulmonary disease should also be studied. All of these studies should include a measure of use of healthcare resources.

Paul Jones, Peter Gibson, Chris Cates, Anna Bara, and Karen Blackhall of the Cochrane Airways Group provided editorial and technical support. Silvana Campanella, Ruth Black, Klaus

Lehnert, and Daniela Screnci translated for us. Further data were provided by Dompe farmaceutici, Zambon Group, and Douglas Pharmaceuticals.

Contributors: PNB initiated the protocol development. PJP and PNB collaborated on every step of both the first review and the update including protocol design, comparisons, data extraction, analysis, interpretation of results, and writing of the paper. PJP is the guarantor.

Funding: None.

Competing interests: None declared.

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(Accepted 28 February 2001)

Reduction in mortality after inappropriate early discharge from intensive care unit: logistic regression triage model

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BMJ 2001;322:1274-6

Abstract

Objective To develop a predictive model to triage patients for discharge from intensive care units to reduce mortality after discharge.

Design Logistic regression analyses and modelling of data from patients who were discharged from intensive care units.

Setting Guy's hospital intensive care unit and 19 other UK intensive care units from 1989 to 1998.

Participants 5475 patients for the development of the model and 8449 for validation.

Main outcome measures Mortality after discharge and power of triage model.

Results Mortality after discharge from intensive care was up to 12.4%. The triage model identified patients at risk from death on the ward with a sensitivity of 65.5% and specificity of 87.6%, and an area under the receiver operating curve of 0.86. Variables in the model were age, end stage disease, length of stay in unit, cardiothoracic surgery, and physiology. In the validation dataset the 34% of the patients identified as at risk had a discharge mortality of 25% compared with a 4% mortality among those not at risk.

Conclusions The discharge mortality of at risk patients may be reduced by 39% if they remain in intensive care units for another 48 hours. The discharge triage model to identify patients at risk from too early and inappropriate discharge from intensive care may help doctors to make the difficult clinical decision of whom to discharge to make room for a patient requiring urgent admission to the unit. If confirmed, this study has implications on the provision of resources.

Introduction

The winter of 1999 highlighted the acute shortage of intensive care beds in the United Kingdom. A consequence of shortage is that patients are often discharged early and perhaps inappropriately to make room for more severely ill patients. A study in 1993 reported mortality after discharge from intensive care from 6.1% to 16.3%.^{1,2} The causes of death after such discharge may be due to factors occurring before^{3,4} or after discharge.⁵⁻⁷ Goldfrad and Rowan, who used

discharges at night as a proxy measure of inappropriate early discharge from intensive care, reported a 1.4-fold increase in ultimate hospital mortality among patients discharged at night.⁸ Patients who died after discharge had significantly higher severity of illness scores or therapeutic intervention scores on the day of discharge than those who survived.^{9,10}

We report on the development of a predictive triage model for discharge to identify patients at risk of dying after discharge from intensive care. We also explored the implications of its use.

Methods

This study was approved by the local ethics committee of Guy's Hospital. We included in the study all patients discharged from the 13 bed intensive care unit at Guy's hospital between 1 June 1990 and 31 December 1998 and from 19 UK units (Riyadh ICU program users group) between June 1989 and September 1996. We analysed daily physiological and treatment data collected prospectively through the Riyadh ICU program (Medical Associated Software House, London) to identify candidate variables for the model. We measured severity of illness and intensity of treatment with the acute physiology and chronic health evaluation (APACHE II) system,¹¹ the organ failure score,¹² and the therapeutic intervention scoring system.¹³ These data, together with demographic data including the presence of chronic ill health (as defined with APACHE II criteria) and patients' hospital outcome, were entered daily on to the computer by a team of specifically trained nurses and doctors.

Model development—There were 6319 patients admitted to the 13 bed general (medical, surgical, and cardiothoracic) adult intensive care unit at Guy's hospital between 30 June 1990 and 31 December 1996. We excluded from the analysis the 844 (13.4%) patients who died on the unit. Only data from the patient's last day in the unit were used to develop the predictive model. We used univariate analysis to identify candidate variables for the model. Variables with a significant influence on survival ($P < 0.05$) after discharge from intensive care were subjected to multivariate logistic modelling. A stepwise forward logistic

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