The therapeutic efficacy of erdosteine in the treatment of chronic obstructive bronchitis: a meta-analysis of individual patient data

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CRD summary
This review found that treatment with erdosteine relieved respiratory symptoms in patients with chronic obstructive bronchitis. Considerable uncertainty surrounded this conclusion as a result of high heterogeneity and reporting and methodological limitations. The results may only be generalisable to adults with exacerbated chronic obstructive bronchitis.

Authors' objectives
To evaluate the efficacy of erdosteine in the treatment of adults with stable or exacerbated chronic obstructive bronchitis

Searching
PubMed and Scirus databases and Google Scholar were searched (dates unspecified) with specified search terms. No language restrictions were applied. The manufacturer of erdosteine was contacted and asked for additional non-indexed publications.

Study selection
Randomised controlled trials that compared erdosteine with placebo or mucolytics in patients with a medical history of chronic bronchitis were eligible for inclusion.

Specified outcomes (recorded after seven to 10 days of treatment) were cumulative global efficacy index (sum of all respiratory symptom scores), cough frequency and intensity, sputum viscosity and purulence, difficulty to expectorate, catarrh ronchi at auscultation and dyspnoea. Individual respiratory symptom scores were based on patient self-assessment using three-point scales. Adverse events were catalogued.

Fifteen eligible studies were identified. Seventy per cent of patients had acute exacerbation of chronic obstructive bronchitis at trial entry. Mean age was 60 years. Erdosteine dose ranged from 150mg to 300mg two or three times daily.

The authors did not state how relevant studies were selected for the review.

Assessment of study quality
Randomisation methods, blinding and description of withdrawals and drop-outs were assessed using the Jadad scale by two independent reviewers. Discrepancies were resolved by consensus.

Use of individual patient data to assess integrity of randomisation, standardise definitions, identify outliers and coding errors or identify attrition was not reported. Contact with trial investigators was not reported.

Data extraction
Individual patient data from trials submitted for European Marketing Authorisation in 2005 were obtained from the manufacturer of erdosteine. The authors did not state whether the extraction was based on individual patient data or aggregate data. Patient characteristics (such as numbers randomised and included in the analysis, age, sex), study endpoints, occurrence and type of adverse events were extracted. Trial-level data relevant to the nature and duration of the intervention and trial validity were extracted.

Methods of synthesis
Summary measures were based on the difference between groups in change from baseline to end of treatment.
Weighted mean differences were calculated using inverse variance methods incorporating random effects. Heterogeneity was tested using Q statistics and measured using $I^2$. Subgroup analyses based on active comparator or placebo were presented.

**Results of the review**

Fifteen trials (1,046 patients) were included in the analysis. Six of the trials were unpublished.

Erdosteine induced a statistically significant reduction in comparison to placebo or mucolytics in cumulative global efficacy index (-1.02, 95% CI -1.60 to -0.44; n=1,046), cough frequency (-0.19, 95% CI -0.34 to -0.03; n=972), cough intensity (-0.30, 95% CI -0.44 to -0.17; n=496), sputum viscosity (-0.28, 95% CI -0.49 to -0.07; n=812), difficulty to expectorate (-0.24, 95% CI -0.40 to -0.08; n=992) and catarrh ronchi at auscultation (-0.35, 95% CI -0.60 to -0.10; n=469). There were no significant reductions for sputum purulence (-0.11, 95% CI -0.28 to 0.07; n=946) and dyspnoea (-0.09, 95% CI -0.24 to 0.07).

Statistically significant heterogeneity was present for all reported outcomes overall and in subgroups based on comparison with mucolytics or placebo with the exception of difficulty to expectorate in comparison to mucolytics. Adverse events (mostly gastrointestinal) were reported by 54 of 529 patients in the erdosteine group and 57 of 517 patients in the comparator group.

**Authors’ conclusions**

Treatment with erdosteine was associated with significant amelioration of symptoms in comparison to placebo or treatment with mucolytics in patients with chronic obstructive bronchitis.

**CRD commentary**

This review aimed to evaluate the efficacy of erdosteine in the treatment of adults with stable or exacerbated chronic obstructive bronchitis. An individual patient data approach (generally regarded as a gold standard for systematic reviews) was used. The proportion of eligible trials for which individual data were available was unclear. The authors reported that they searched several databases. No flow diagram of article inclusion and exclusion was presented. All of the included studies were supplied by the manufacturers, which made evaluation of potential bias difficult. The inclusion of two non-randomised trials was inconsistent with the stated eligibility criteria.

The authors did not report how individual patient data were used to standardise definitions of outcomes and subgroups, generate effects across trials in a consistent manner and verify the validity of raw data. Individual patient covariates were not included in subgroup analyses and trial level covariates were not subject to interaction tests. It was, therefore, impossible to preclude the potential operation of selection biases within and across trials and identify any realised benefits of an individual patient data approach. Additional uncertainty came from high heterogeneity within results and a lack of clear definition of clinical significance.

The issues outlined resulted in considerable uncertainty about the reliability of the author's conclusions. Most patients had exacerbated chronic obstructive bronchitis at baseline and it was unclear how well the review findings generalised to other populations.

**Implications of the review for practice and research**

**Practice:** The authors stated that the review supported use of erdosteine in combination with standard therapy in respiratory diseases characterised by increased expectoration.

**Research:** The authors stated that larger long-term studies with fully validated endpoints were required.

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