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

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ABSTRACT

Erdosteine, a drug approved for the treatment of acute and chronic pulmonary diseases, has been shown to be an effective treatment for chronic bronchitis or COPD (CB/COPD) in several studies, although marked differences in the perception of its usefulness still remain.

Aim: to test the available evidence for the efficacy of erdosteine in adults with stable or exacerbated CB/COPD.

Methods: Meta-analysis of individual patient data from both published and unpublished randomized controlled trials (RCTs) comparing erdosteine with placebo/mucolytics, given for up to 10 days in association with standard therapy (RCTs used for regulatory drug approval). Individual patient data were provided by the manufacturer of erdosteine, Edmond Pharma (Milano, Italy). Endpoints were symptom scores (cough frequency and intensity, sputum viscosity and purulence, difficulty to expectorate, catarrh rhonchi at auscultation, dyspnoea), a cumulative global efficacy index (cGEI), and an overall physician efficacy assessment (OA).

Results: individual data from 1046 patients from 15 RCTs (12 on exacerbated and 3 on stable CB/COPD) were obtained. Erdosteine induced a significant reduction of cGEI vs comparators (−1.02; 95% CI: from −1.60 to −0.44; $p = 0.0006$), both placebo and mucolytics. On individual symptoms, it positively impacted on cough frequency (−0.19; 95% CI: from −0.34 to −0.03) and intensity (−0.30; 95% CI: from −0.44 to −0.17), sputum viscosity (−0.28; 95% CI: from −0.49 to −0.07), difficulty to expectorate (−0.24; 95% CI: from −0.40 to −0.08), and catarrh ronchi at auscultation (−0.35; 95% CI: from −0.60 to −0.10). The effects on dyspnoea were only significant vs placebo, whereas sputum purulence was not significantly modified. The OA also favoured erdosteine, doubling the chance of success compared with placebo and mucolytics: OR (odds ratio) 2.06; (95% CI: from 1.27 to 3.33). The treatment with erdosteine was well tolerated. Adverse events, mainly gastrointestinal, were reported by 10.2% of patients compared to 11.0% in the reference groups.

Conclusions: Treatment with erdosteine is associated with a significant benefit in terms of symptom amelioration both vs placebo and mucolytics in patients with CB/COPD. Although with some limitations (e.g. not fully validated scores) this review reinforces the use of erdosteine, in combination with standard therapy, in respiratory diseases characterized by increased expectoration, namely acute CB/COPD exacerbations.

1. Introduction

Chronic bronchitis (CB) is very often associated with airflow obstruction and is especially frequent in smokers, is considered to contribute to the airway mucus hypersecretory component of Chronic Obstructive Pulmonary Disease (COPD) [1], and is associated with considerable morbidity and high health-care costs [2]. Patients with chronic bronchitis and COPD suffer from recurrent exacerbations, with an increase in volume and/or purulence of sputum, cough and dyspnoea which contribute to progressive clinical deterioration and account for a significant proportion of the cost of caring for such patients [3–5].

There is evidence for inflammatory and morphological changes in the airways associated with loss of ciliary function and mucus

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gland hyperplasia, and the importance of mucus in contributing to airflow limitation and disease progression are underscored by recent studies [6,7].

The use of mucolytics as adjunctive treatment of both stable and exacerbated CB/COPD has been proposed to improve disease outcome, although the value of the use of such drugs is still considered uncertain [8].

Erdosteine is a a drug approved for the treatment of acute and chronic pulmonary diseases for more than 10 years which has been shown to improve sputum rheology in patients with mucus hypersecretion through an active metabolite (Met-I) having free thiol groups [9]. Although a few studies have been published showing that CB/COPD patients may benefit from erdosteine, marked differences in the perception of its usefulness still remain.

The aim of the present systematic review is therefore to test the available evidence that erdosteine treatment in patients with CB/COPD may be effective and accompanied by clinically relevant improvements.

2. Methods

This systematic review was performed in accordance with the Quality of Reporting of meta-analyses (QUORUM) guidelines [10].

3. Types of studies

Randomized controlled trials (RCTs) focusing on the comparison between erdosteine and placebo or mucolytics which reported data on efficacy and safety after 7–10 days of treatment, were used for this meta-analysis.

4. Types of patients

Adults patients having a medical history of chronic bronchitis (CB), generally defined as the presence of cough and sputum production for at least three months a year over two consecutive years were included in the studies used in this meta-analysis. The three largest studies also included evidence for airway obstruction, defined as an FEV_1/FVC ratio at least 10% below the normal theoretical value [11–13].

Patients were enrolled either at occurrence of an acute exacerbation or during the stable phase of the disease. The diagnosis of acute exacerbations was based on the occurrence of increased mucopurulent sputum, cough and fever. Three studies additionally included the isolation of antibiotic-sensitive bacterial strains in sputum [11,14,15]. In two studies the inclusion of patients with hypersecretory acute bronchitis was also allowed [15,16].

5. Type of intervention

Erdosteine (300 mg capsule) was administered two or three times daily on top of background therapy, generally antibiotics and bronchodilators (β_2-agonists and aminophyllines) in patients with acute exacerbations, and bronchodilators in those with stable disease.

Placebo or mucolytics (ambroxol, *N*-acetylcysteine, carbocysteine, sobrerol) were administered with the same dosing schedules as erdosteine (i.e. two or three times daily) on top of background treatments.

6. Type of outcome measures

The following outcomes were investigated: i) cumulative global efficacy index (cGEI), the sum of all assessed respiratory symptom scores, ii) respiratory individual symptom scores (cough frequency and intensity, sputum viscosity and purulence, difficulty to expectorate, catarrh rhonchi at auscultation, dyspnoea), iii) overall assessment of efficacy (OA) by the Investigator, and frequency of adverse events. In the original studies, similar scoring systems were used for patient self-assessment of symptoms, usually categorised on a 0–3 scale from 0 = absent to 3 = worst.

In particular: *cough frequency* 1 = sporadic fits/mild/occasional, 2 = repeated diurnal fits/ moderate/frequent, 3 = repeated diurnal and sleep disturbed/severe/continuous; *cough intensity* 1 = mild/not disturbing, 2 = moderate/fairly disturbing, 3 = severe/severely disturbing; *sputum viscosity* 1 = fluid almost watery, 2 = moderately viscous, 3 = viscous & thick; *sputum purulence* 1 = mucoid whitish, 2 = mucopurulent yellowish, 3 = purulent intensely yellow; *difficulty to expectorate* 1 = sometimes/easy at first cough fit/mild, 2 = often/with some effort/moderate, 3 = always/with considerable effort/severe; *catarrh ronchi at auscultation* 1 = mild, 2 = moderate, 3 = severe/remarkable; *dyspnoea* 1 = at fast walk/with moderate exertion, 2 = at regular walk/with minimal exertion, 3 = at slightest effort/at rest. Categories were considered comparable.

In one study [12], the symptoms of cough frequency and intensity, difficulty to expectorate and dyspnoea were assessed on a 5-point scale.

The Investigator's OA was based on 0–3 scale, with 0 = none/poor, 1 = fair/modest, 2 = good, 3 = excellent/return to normality. In three studies [16–18] efficacy was judged as negative, doubtful or positive, and in one study [12] a 5-point scale was used (none, poor, moderate, good, excellent).

In all the studies, safety was evaluated in terms of incidence of adverse events reported during treatment, with particular regard to gastrointestinal complaints.

7. Study search

Literature was search systematically for relevant clinical trials with no language restrictions (Pub Med, Google Scholar and Scirus with search terms "chronic bronchitis", "COPD" and "acute exacerbations" combined with "erdosteine"). Furthermore, the manufacturer of erdosteine (Edmond Pharma s.r.l., Italy) was contacted and asked for any additional non-indexed publications and relevant unpublished studies. Individual patient data from the published and unpublished studies in patients with CB submitted for European marketing approval in 2005 were considered.

8. Data extraction

For each of the selected trials, the following information was retrieved: first author, publication year, details of study design, studied treatments (type of drug, schedule, duration), patient characteristics (total number, age and sex distribution, number randomized and number included in the analysis), study endpoints, occurrence and type of adverse events.

The quality of the selected trials was assessed according to a five-point validated scale [19] measuring a range of factors that impact the quality of a trial: randomization methods, blinding and description of withdrawals and dropouts. Two independent reviewers assessed the quality of the trials to be included. Differences in the evaluation were resolved by consensus, referring back to the original article/report.

9. Statistical analysis

Trials were grouped according to the type of erdosteine comparator (active or placebo), study quality (Jadad scale score 1–2 vs 3–4–5) and whether the study was published or not.