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Impact of erdosteine on chronic bronchitis and COPD: A meta-analysis

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ABSTRACT

A previous meta-analysis suggested that the treatment with erdosteine was associated with significant amelioration of the cumulative global efficacy index and symptoms in comparison to placebo or other mucolytics. However, this conclusion was criticized because the meta-analysis, as it had been done, made it impossible to preclude the potential operation of selection biases within and across trials, and identify any realised benefits of an individual patient data approach. Taking into consideration these criticisms and also the publication of two further recent articles focused on the prevention of chronic obstructive pulmonary disease (COPD) exacerbations with erdosteine, we have carried out a quantitative synthesis via meta-analysis of the currently available data on the use of this drug. Our findings included data from ten studies involving 1278 patients and show that erdosteine is able to improve the clinical score of patients with chronic bronchitis and COPD, and also reduces the overall risk of chronic bronchitis/COPD exacerbations, and reduces the risk of experiencing at least one exacerbation. Furthermore, our data suggest that erdosteine can lengthen the time to the first COPD exacerbation, reduce the duration of a COPD exacerbation and the risk of hospitalization from COPD. The documented effect of erdosteine in reducing the occurence and/or influencing COPD exacerbations is important because it indicates that erdosteine can be added to the list of drugs that can be recommended for treating COPD.

1. Introduction

Mucoactive agents, mucolytics and/or mucoregulators, have two main targets, namely to decrease the mucus hypersecretion and alterations in the oxidant/antioxidant balance in respiratory diseases such chronic bronchitis and COPD [1].

Making mucus easier to expectorate would seem a sensible goal in the treatment of COPD because it has been shown that mucus hypersecretion is associated with greater susceptibility to develop COPD, an accelerated annual decline in forced expiratory volume in 1 s (FEV_1), hospitalisations and excess mortality [2]. However, also oxidative stress is an important feature of chronic bronchitis and COPD [3] and therefore targeting oxidative stress or boosting the endogenous levels of antioxidants is likely to be beneficial as an additional pharmacological approach to the treatment of COPD patients [3].

Many mucolytic agents, such as N-acetyl-L-cysteine, N-acystelyn, erdosteine, fudosteine, ergothioneine, and carbocysteine lysine salt, belong to the cysteine family of drugs are also known to possess potentially important antioxidant properties [4].

Erdosteine [*N*-(carboxymethylthioacetyl)-homocysteine thiolactone] is a drug originally developed as mucolytic agent which is used in many Countries since 1995 as a treatment of chronic bronchitis and COPD [5]. Erdosteine acts by breaking the disulfide bonds of mucus glycoproteins, affecting the physical properties of the mucus, thus leading to increased mucus clearance [5]. It also acts as an antioxidant through free radical scavenging [6]. Furthermore, erdosteine elicits an anti-inflammatory activity documented by a significant reduction in the levels of pro-inflammatory eicosanoids and cytokines in the blood of COPD patients [7] and in the release of inflammatory mediators due to the exercise-induced oxidative stress in severe COPD patients [8]. Importantly, erdosteine also has antibacterial effects through reducing bacterial adhesiveness [9].

In 2010, some of us performed a meta-analysis to test the available evidence that erdosteine treatment in patients with chronic bronchitis/COPD might be effective and accompanied by clinically relevant improvements [10]. Fifteen trials (1046 patients) were included in the analysis. Treatment with erdosteine was associated with a significant amelioration of the cumulative global efficacy index and symptoms in comparison to placebo or treatment with other mucolytics, but we concluded that larger long-term studies with fully validated endpoints were required.

The Centre for Reviews and Dissemination (CRD), an international

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centre engaged exclusively in evidence synthesis in the health field, determined that this meta-analysis met the Database of Abstracts of Reviews of Effects (DARE) scientific quality criteria for a systematic review [11]. However, in their comments, they highlighted that the article did not present a flow diagram of article inclusion and exclusion. All of the included studies were supplied by the manufacturers, which made evaluation of potential bias difficult. They also pointed out that we 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 the 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.

In light of these criticisms and the recent publication of two further articles focused on the prevention of acute exacerbations of COPD and ability to reduce their duration with erdosteine [12,13], we have carried out a quantitative synthesis via meta-analysis of the currently available data with this drug in order to provide consistent and homogeneous findings that may help better clarify the real impact of erdosteine in improving the clinical score of patients with chronic bronchitis and/or COPD, and the use of this drug in preventing chronic bronchitis/COPD exacerbations.

2. Methods

2.1. Search strategy

This meta-analysis has been registered in PROSPERO (registration number: CRD42017068372), and performed in agreement with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement (Fig. 1) [14]. Furthermore, this synthesis satisfied all the recommended items reported by the PRISMA-P 2015 checklist [15].

We undertook a comprehensive literature search for studies evaluating the impact of erdosteine on chronic bronchitis and/or COPD. In particular, the term “erdosteine” was searched for the active treatment, and the terms “chronic bronchitis” OR “chronic obstructive pulmonary disease” OR “COPD” were searched for the diseases. The search was performed in PubMed, Scopus, Embase, Google Scholar and the repository database clinicaltrials.gov [16] to provide relevant studies published up to July 31, 2017. No language restriction was applied. Citations of previously published meta-analyses and relevant reviews were examined to identify further pertinent studies, if any [5,9,10,17–19].

2.2. Study selection

Studies reporting the effect of erdosteine vs. placebo/control/baseline in patients with chronic bronchitis and/or COPD have been selected. All studies assessing the impact of erdosteine on clinical score (s) and the rate of exacerbations of chronic bronchitis and/or COPD have been included in the analysis. No restriction on the duration of the treatment was applied.

Two reviewers independently checked the relevant studies identified from the literature searches and databases. Studies were selected in agreement with the previously mentioned criteria, and any difference in opinion about eligibility was resolved by consensus.

2.3. Data extraction

Data from included studies were extracted and checked for study characteristics and duration, doses of medication, patient characteristics, age, gender, smoking habits, FEV_1, Jadad score, clinical score, and exacerbation and hospitalization rates.

2.4. Endpoints

The primary endpoint of this quantitative synthesis was the impact of erdosteine on the clinical score of patients with chronic bronchitis and/or COPD, and the rate of exacerbations, compared to control values in placebo/control groups, or at baseline. The secondary endpoint was the influence of erdosteine on the duration of exacerbation and rate of hospitalization.

2.5. Quality score, risk of bias and evidence profile

The Jadad score, with a scale of 1–5 (score of 5 being the best quality), was used to assess the quality of the randomized clinical trials (RCTs) concerning the likelihood of biases related to randomization, double blinding, withdrawals and dropouts [20]. Two reviewers independently assessed the quality of individual studies, and any difference in opinion about the quality score was resolved by consensus.

The risk of publication bias was assessed by applying the funnel plot and Egger's test through the following regression equation: $SND = a + b \times precision$, where SND represents the standard normal deviation (treatment effect divided by its standard error [SE]), and precision represents the reciprocal of the standard error. Evidence of asymmetry from Egger's test was considered to be significant at $P < .1$, and the graphical representation of 90% confidence bands are presented as described elsewhere [20].

The optimal information size (OIS) was calculated as previously reported [21,22], and the quality of the evidence assessed in agreement with the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system [23]. The risk of publication bias and GRADE analysis were performed on the effect estimates resulting from at least 3 high-quality studies (Jadad ≥ 3).

2.6. Data synthesis and analysis

Results of this pair-wise meta-analysis are expressed as Standardized Mean Difference (SMD), Relative Risk (RR), Natural Logarithmic transformed Proportion (Log Proportion, PLN) and 95% confidence interval (95%CI).

The changes in clinical score are reported as SMD since this outcome was not always standardized among the studies (i.e. cumulative Global Efficacy Index [cGEI], breathlessness–sputum–cough scale [BCS], Subject's Global Assessment of Disease Severity [SGADS], Physician's Global Assessment of Disease Severity [PGADS], and non-specific clinical score [NSCS]). The risk of COPD exacerbation and hospitalization are reported as RR, and normalized as a function of person-season, where one season includes 3 months [24]. The time to first exacerbation and the duration of exacerbation are reported as PLN. Moderate to high levels of heterogeneity were considered for $I^2 \geq 50\%$ [16].

Since data were selected from a series of studies performed by researchers operating independently, and a common effect size cannot be assumed, the random-effects model was used in order to balance the study weights and to adequately estimate the 95%CI of the mean distribution of the effect of the active medication on the investigated variables [24].

Subset analyses were performed by excluding the low-quality studies characterized by Jadad score < 3, and considering specifically patients affected by chronic bronchitis and/or COPD.

OpenMetaAnalyst [25] software was used for performing the meta-analysis, GraphPad Prism (CA, US) software to graph the data, and GRADEpro to evaluate the quality of evidence [23]. The statistical significance was assessed for $P < .05$.