Pulmonary Pharmacology & Therapeutics 33 (2015) 47–51

Contents lists available at ScienceDirect

Pulmonary Pharmacology & Therapeutics

journal homepage: www.elsevier.com/locate/ypupt

Efficacy of erdosteine 900 versus 600 mg/day in reducing oxidative stress in patients with COPD exacerbations: Results of a double blind, placebo-controlled trial

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ARTICLE INFO

Article history:
Received 30 March 2015
Received in revised form
19 June 2015
Accepted 22 June 2015
Available online 23 June 2015

Keywords:
Erdosteine
Chronic obstructive pulmonary disease
COPD exacerbations
Airway inflammation
Oxidative stress
Antioxidants

ABSTRACT

Background: Acute exacerbations of chronic obstructive pulmonary disease (AECOPD) are associated with increased airway and systemic inflammation. There is evidence that erdosteine accelerates recovery from AECOPD by reducing airway inflammation.
Aim: To investigate the dose-dependent antioxidant/anti-inflammatory activity of erdosteine in COPD patients.
Methods: In this single-centre, double blind, double dummy study, patients with mild-to-moderate COPD (GOLD stage II–III), were randomised to receive either placebo or two dosages of oral erdosteine (300 mg tid or 300 mg bid + 1 capsule of indistinguishable placebo) for 28 days in addition to their standard treatment. Primary variables were plasma reactive oxygen species (ROS) and 8-isoprostane levels, while secondary variable was lung function (FEV1; FEV1/FVC; FEV1 short-term reversibility), all assessed in baseline; every two weeks during the study, and one week after the end of the study.
Results: Baseline demographic characteristics, plasma ROS and 8-isoprostane levels and lung function were not significantly different in the 24 eligible patients (14 males, aged 38–75 years). At 2 weeks, there was a dose-dependent decrease in ROS in the erdosteine groups. By week 4 there were significant differences in ROS levels compared to baseline between patients receiving 900 mg/day ($p < 0.003$) and those receiving 600 mg/day ($p < 0.04$). This effect continued in the follow-up week ($p < 0.021$). Erdosteine also lowered 8-isoprostane plasma levels after 4 weeks ($p < 0.01$), and this effect lasted over the post-treatment week. Moreover, % FEV1 reversibility after salbutamol 400 mcg obtained after a 4 -week treatment of erdosteine 900 mg/day was significantly higher than that obtained after 600 mg/day ($p < 0.01$). Erdosteine was well tolerated and no treatment-related adverse event was reported.
Conclusions: Results confirm the antioxidant dose- and time-dependent activity of erdosteine, and support the utility of including erdosteine it in the therapeutic strategy for the prevention and treatment of oxidative stress-induced inflammation, which frequently leads to AECOPD occurrence.

1. Introduction

The prevalence of chronic obstructive pulmonary disease (COPD), a preventable and treatable condition, is forecast to increase in the coming decades due to the cumulative effects of people's increasing exposure to risk and ageing factors [1]. COPD is currently the fourth leading cause of mortality worldwide with an estimated 2.75 million deaths—a figure set to double by 2030 [2]. COPD represents a major challenge for public healthcare systems—in Europe, 56% of the overall budget for respiratory diseases is spent for the COPD management, and in the USA the combined direct and indirect costs of COPD reach a staggering $50 billion [3,4]. In Italy, the economic impact of COPD approached one point of gross domestic product (GDP) in 2014 [5]. Acute exacerbations of COPD (AECOPD), such as episodes of worsening of patients' daily symptoms, cause substantial morbidity and mortality, and

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http://dx.doi.org/10.1016/j.pupt.2015.06.004
1094-5539/

consume the largest percentage of the total cost of COPD [5–7]. As the condition deteriorates, costs increase progressively. COPD and AECOPD are not only costly to treat but cause significant disability, with estimates indicating that COPD will become the seventh leading cause of DALYs (disability-adjusted life years) lost worldwide in 2030 [7].

COPD is a complex condition due to its multifactorial pathogenesis and although our knowledge of its mechanisms, has dramatically improved in recent years, COPD progresses and progressively reduces quality of life (QoL) and survival. AECOPD symptoms (such as increased breathlessness, cough, mucus production, extreme fatigue) are associated with increased airway and systemic inflammation in the lungs [8–10]. Essentially, the inflammatory response of the respiratory tract to chronic irritants (i.e. cigarette smoke) is amplified. Oxidative stress, as indicated by increased levels of biomarkers (in particular, hydrogen peroxide and 8-isoprostane), further increases inflammation. AECOPD are also triggered by respiratory viruses and bacteria, which enter the airways and further increase inflammation. These agents, together with a reduction in endogenous antioxidants, are frequently the cause of hospital admission and are associated with a high risk of recurrence [2,11]. AECOPD remain a significant area of unmet medical need, and prevention and treatment of AECOPD represent key treatment goals [2].

Erdosteine is a mucoactive agent with antioxidant and anti-inflammatory effects which also enhances the activity of antibiotics and protects against the damage caused by oxidative stress [12,13]. Actually, it has been shown that erdosteine significantly decreases the levels of reactive oxygen species (ROS) and reduces pro-inflammatory cytokines (IL-8) and 8-isoprostane, in the peripheral blood of COPD patients who smoked [14]. In stable COPD, long-term treatment with erdosteine is associated with a reduction in acute exacerbations and hospitalizations, and significant improvements in QoL. A recent meta-analysis supported the effectiveness of erdosteine in patients with COPD, in particular during acute exacerbations, while other studies indicate that erdosteine 900 mg/day added to concurrent standard treatment improves outcomes in patients with AECOPD. Moreover, the antioxidant activity of erdosteine has been documented as able to accelerate recovery by reducing the burst of airway inflammation [15–17]. Finally, experimental and clinical evidence suggest that erdosteine may be most beneficial in patients who have repeated, prolonged, or severe AECOPD [18].

The present study was designed to investigate the dose-dependency of antioxidant/anti-inflammatory activity of erdosteine in patients with COPD.

2. Materials and methods

2.1. Study design

This was a single-centre, randomized, double blind, double dummy, placebo-controlled trial. The study was carried out in accordance with Good Clinical Practice (GCP) guidelines and conformed with the Declaration of Helsinki 1964, as currently amended.

2.2. Patients

Male and female patients (aged 38–75 years) with mild-to-moderate COPD (GOLD stage II–III) were eligible for inclusion.

2.2.1. Exclusion criteria

- Women of child-bearing age not using adequate contraception, pregnant women and those lactating.
- Presence of concomitant clinically relevant conditions (uncontrolled diabetes, serious hepatic/renal failure, lung cancer, tuberculosis, cystic fibrosis, uncontrolled cardiac conditions etc.).
- Previous hospitalization(s) for AECOPD.
- Antibiotic/corticosteroid treatment in previous 4 weeks.
- Participation in a clinical trial in preceding 3 months.

2.3. Treatments

Patients were randomized to receive for 28 days one of following treatments on top of their standard daily treatment (i.e. bronchodilators): 1) placebo; 2) oral erdosteine 300 mg tid; 3) erdosteine 300 mg bid +1 capsule of indistinguishable placebo. Erdosteine as marketed in Italy, was kindly supplied by Edmond Pharma srl. Treatment with other mucoactive agents (N-acetylcysteine, carbocisteine, ambroxol, etc.) and cough suppressants (codeine, dropropizine, dextromethorphan, etc.) was not permitted during the study period.

2.4. Measurements

Lung function and % FEV1 short-term reversibility to salbutamol 400 mcg were assessed at the study entry; every two weeks until the end of the study, and one week after discontinuation of treatments to assess any possible carry-over effect. Plasma levels of ROS and 8-isoprostane were measured at the same experimental times.

2.5. Variables

Primary efficacy variables were plasma ROS and 8-isoprostane levels, while secondary variables were indices of lung function (i.e. FEV1; FEV1/FVC; % FEV1 short-term reversibility to salbutamol 400 mcg). Plasma ROS concentrations were measured immediately after blood collection using a monochromatic light absorbency spectrophotometer at a constant temperature of 37 °C (Callegari, Parma, Italy). Values were expressed as Fort Units (1 FU, the oxidative power of 0.26 mg/L H_2O_2), being normal values $\leq$300FU [14]. Plasma 8-isoprostane concentrations were measured using an automated immunoanalyzer (Immulite, DPC, USA), values being expressed as pg/mL [14]. Lung function was determined by a CPFS/D spirometer (Medical Graphics Co.; Oak Grove Parkway, St. Paul, Minnesota, USA).

2.6. Statistical analyses

Results were statistically compared according to the general linear model procedure. Analysis of variance (ANOVA) was used to compare the three treatment arms, and t tests to compare means ± SD; $p < 0.05$ was accepted as the lowest level of significance.

3. Results

Twenty-four patients (8 for each arm) completed the study protocol and were eligible for analysis (Table 1). The demographic characteristics of patients in the three arms were well matched in baseline. ROS plasma levels were absolutely comparable within the three groups in baseline (Table 2, Fig. 1). After 2 weeks there was a dose-dependent decrease in ROS plasma levels in both erdosteine-treated arms (600 and 900 mg/day), and both trends proved