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Erdosteine: Antitussive and Anti-inflammatory Effects

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Abstract Erdosteine is a multifactorial drug currently used in COPD for its rheologic activity on bronchial secretions and its positive effects on bacterial adhesiveness. Erdosteine produces an active metabolite (Met 1) which was shown to produce antioxidant effects during the respiratory burst of human PMNs, due to the presence of an SH group. The substantial antitussive effects of erdosteine were first documented in clinical trials even though mucolytic agents are regarded as not consistently effective in ameliorating cough in patients with bronchitis, although they may be of benefit to this population in other ways. Actually, a mucolytic drug could exert antitussive effects if it also affects mucus consistency and enhances ciliary function. In the last decade, data from several studies on animal models pointed to the possible antitussive and anti-inflammatory properties of erdosteine and an indirect anti-inflammatory mechanism of action was suggested. Recently, data from some controlled versus placebo studies documented the antioxidant properties of erdosteine in humans and in current smokers with COPD. The mechanism of action was described as related to erdosteine's ability to inhibit some inflammatory mediators and some pro-inflammatory cytokines that are specifically involved in oxidative stress. As oxidative stress is also presumed to impair β-adrenoceptor function and contribute to airway obstruction, specific controlled studies recently investigated the effect of antioxidant intervention on short-term airway response to salbutamol in nonreversible COPD, according to a double-blind design versus placebo and NAC. Only erdosteine consistently restored a significant short-term reversibility in COPD subjects, previously unresponsive to β_2 adrenergics. This peculiar activity of erdosteine (to our knowledge never previously assessed) proved related to the ROS scavenging activity (which actually proved equal to that of N), and its significant inhibiting effect on lipoperoxidation (8-isoprostane) proved discriminant between treatments, with antioxidant and anti-inflammatory effects the main determinants of the erdosteine multifactorial properties. In addition, antitussive effects may be regarded as related to its anti-inflammatory properties via the improvement of mucociliary clearance and the reduction of chemokines from epithelial cells. Finally, a sort of "sensitization" of 2-adrenoceptors can also be speculated due to the same mechanisms of action; if confirmed by further controlled studies, this particular property would suggest a novel therapeutic role of erdosteine in COPD.

Keywords Erdosteine · Cough · Airway inflammation · Oxidative stress

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Erdosteine is a multimechanism substance that is currently used in chronic obstructive pulmonary disease (COPD) because of its rheologic activity on bronchial secretions and its positive effects on bacterial adhesiveness [1–4]. Erdosteine has a thiol group in a lactone ring which becomes available for pharmacologic activity after its metabolization to the active species called Metabolite1 (Met 1) (Fig. 1). Met 1 has been shown to inhibit nitric oxide, superoxide, and peroxynitrite production *in vitro* during the respiratory burst of human neutrophils [2]. The substantial antitussive effects of erdosteine were first documented in clinical trials [5–8], even though mucolytic agents are still regarded as not consistently effective in ameliorating cough in patients with bronchitis; however,

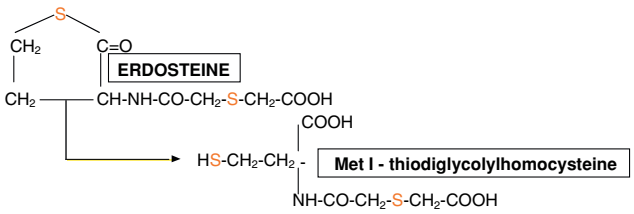

Fig. 1 Chemical structure and metabolic pathway of erdosteine

they are considered beneficial to this population in other ways [9]. Actually, it is suggested that a mucolytic drug could exert antitussive effects if it also affects mucus consistency and enhances ciliary function [9]. In particular, a significant enhancement of mucociliary clearance was seen in both human and animal models during erdosteine treatment, but not during placebo [10, 11] (Fig. 2).

In the last decade several studies on animal models pointed at the possible antitussive and anti-inflammatory properties of erdosteine [11, 12] and an indirect anti-inflammatory mechanism of action was suggested [12]. Recently, data from some control-versus-placebo trials documented the antioxidant properties of erdosteine in humans and in current smokers with COPD [13, 14].

Two years ago, a 10-day course with erdosteine at 900 mg/day proved effective in significantly reducing reactive oxygen species (ROS) level in peripheral blood of stable COPD patients who smoke, together with the level of some chemotactic cytokines (IL-6 and IL-8) in their bronchial secretions. Erdosteine induced a substantial drop in the concentration of both ROS and cytokines after a 4-day treatment [15]. The results of this preliminary open study have been confirmed by a recent double-blind, placebo-controlled trial carried out in stable COPD subjects (GOLD class 0–2) treated with erdosteine 600 mg/day. In particular, a significant and substantial reduction in the level of 8-isoprostane (a product of lipid peroxidation) was also documented in the erdosteine group only [16] since day 7 of treatment.

From these pivotal studies, the main mechanism of action of erdosteine was suggested as likely related to its ability of inhibiting some inflammatory mediators and some proinflammatory cytokines that are specifically involved in oxidative stress and in cell membrane damage [16] (Figs. 3–5).

More recently, as oxidative stress is also presumed to impair β-adrenoceptor function and then contribute to airway obstruction, a specific controlled study was carried out to investigate the possible effect of antioxidant intervention on short-term airway response to salbutamol in nonreversible COPD, according to a double-blind design versus placebo and NAC [17]. Changes obtained with the different treatments in baseline and after 4 and 10 days were compared statistically over time. Only erdosteine proved able to consistently restore a significant short-term reversibility in COPD subjects (6–7% from baseline) who were previously unresponsive to β_2 adrenergics (Fig. 6). Interestingly, the kinetics of FEV_1 changes (such as of reversibility in airway obstruction) observed in all groups of subjects was

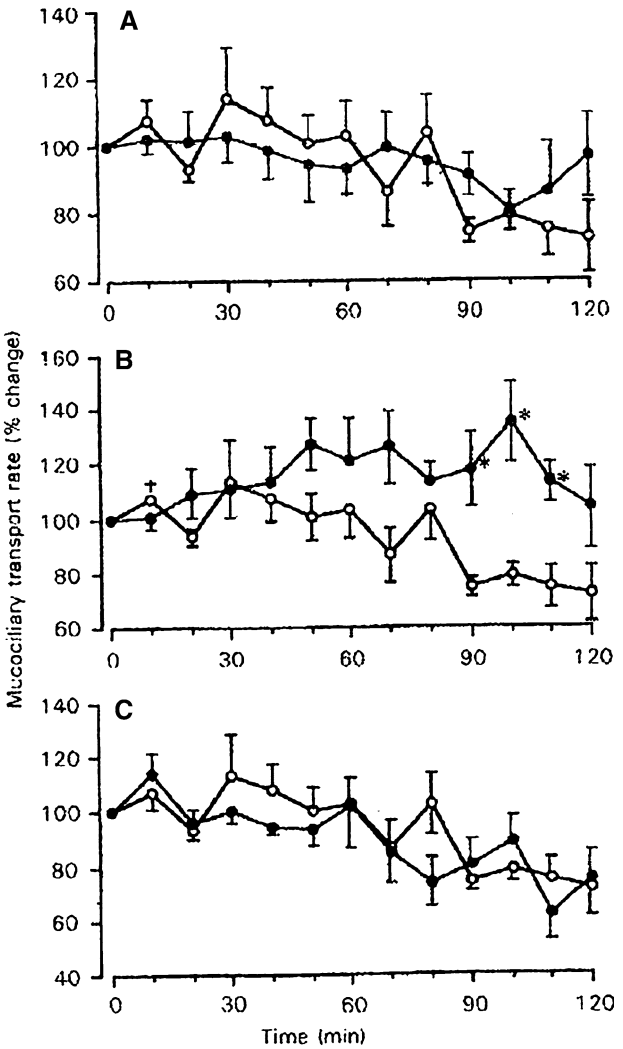

Fig. 2 Effect of erdosteine on mucociliary clearance [from 12]

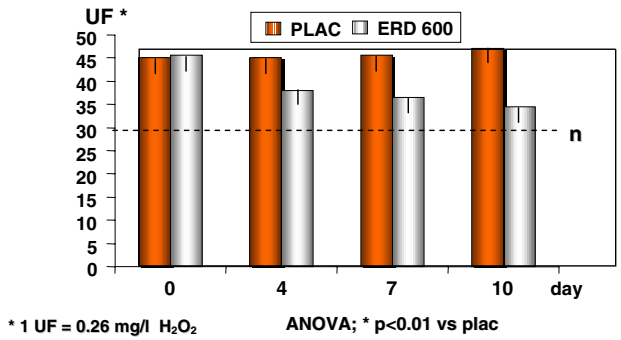

Fig. 3 Changes of ROS levels in blood following erdosteine 600 mg/day and placebo [from 16]

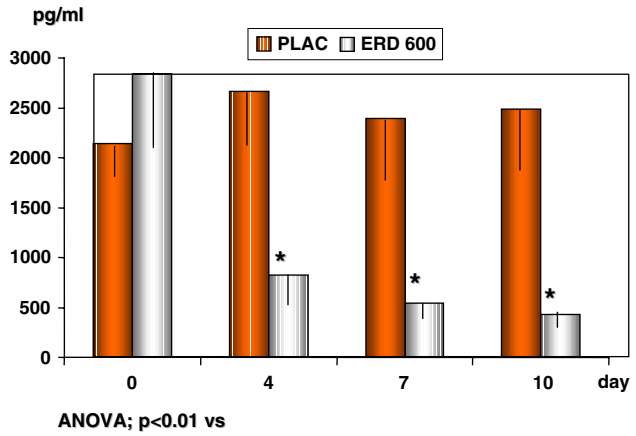

Fig. 4 Changes of IL-8 levels in bronchial secretions following erdosteine 600 mg/day and placebo [from 16]

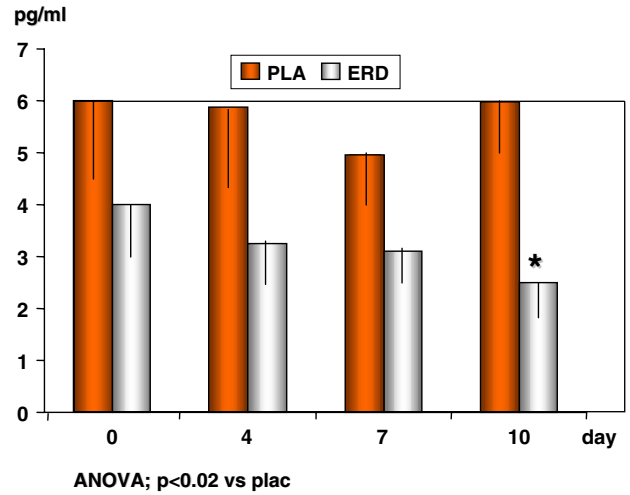

Fig. 5 Changes of 8-isoprostane levels in blood following erdosteine 600 mg/day and placebo [from 16]

shown to be related to the corresponding changes in 8-isoprostane levels. Moreover, this peculiar activity of erdosteine (to our knowledge never previously assessed) proved related to the scavenging effect on ROS of this molecule (which was in fact equal to that of NAC). Actually, even though erdosteine has a much lower molecular weight, it showed a stronger and significant inhibitory action on lipoperoxidation (which is mirrored by the substantial drop in 8-isoprostane level). This effect proved highly discriminant between treatments and was able to explain the antioxidant and anti-inflammatory properties of erdosteine, which likely represent the main determinants of its multifactorial therapeutic potential. At present, the antitussive effects of erdosteine should be regarded as related to its anti-inflammatory activities via the improvement of mucociliary clearance and the reduction of chemokines from epithelial cells.

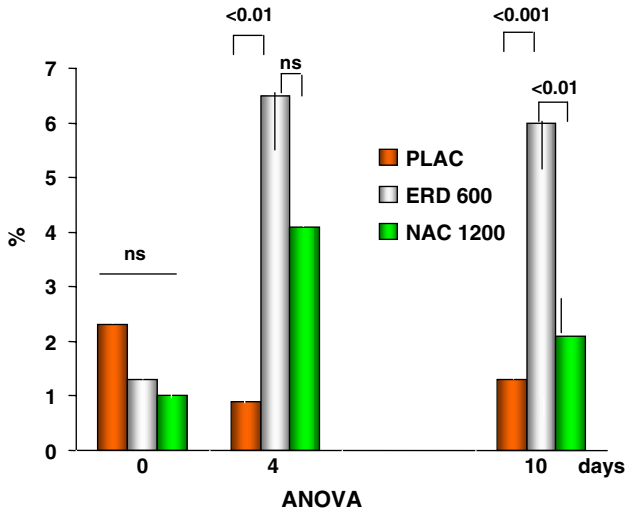

Fig. 6 FEV_1 reversibility (% changes in FEV_1 vs. baseline) following a 10-day course of erdosteine 600 mg/day; NAC 1200 mg/day, and placebo in COPD subjects [from 17]

Finally, it can be speculated that a sort of "resensitization" of β_2-adrenoceptors likely occurs according to the above-mentioned mechanisms of action. If confirmed by further controlled studies, this particular property would suggest a novel therapeutic role of erdosteine in long-term treatment of COPD, particularly in smokers.

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