Short Review

Ambroxol … more than an expectorant

The benefit of using ambroxol in chronic respiratory diseases?

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ABSTRACT
Chronic respiratory diseases comprise of chronic obstructive pulmonary disease (COPD), asthma, occupational lung diseases and bronchiectasis, amongst others. Most of these long-term diseases are not curable and cause an enormous economic burden. Mucoregulators such as ambroxol have been used for decades as a treatment for pulmonary diseases, in order to reduce the burden of the disease and improve quality of life by promoting mucus clearance. Effects of ambroxol include the increase of surfactant production, cytokine reduction and counteracting of oxidative stress in the lungs. Positive effects of ambroxol have been described *in vitro* and in clinical studies for COPD, chronic bronchitis as well as in acute respiratory infections. In addition, antiviral, antibacterial and antifungal properties have been demonstrated. Ambroxol has a good safety profile. In this short review article, the current clinical knowledge on Ambroxol is summarized.
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Key words:
- Chronic bronchitis
- Chronic obstructive lung disease
- COPD
- CRD
- Ambroxol
- Anti-inflammatory therapy
- Bronchiectasis
- Mucoactive
- Antibiotics
- Common cold

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Chronic respiratory diseases (CRDs) are mainly diseases of the airways and lung parenchyma and are responsible for high individual and economic costs. Some of the most common are chronic obstructive pulmonary disease (COPD), asthma, occupational lung diseases and bronchiectasis. In addition to tobacco smoke, other risk factors include air pollution, occupational chemicals and dusts, and frequent lower respiratory infections during childhood. Most CRDs are not curable, however, various forms of treatment that help dilate major air passages and improve shortness of breath help in the control of symptoms, reduce the toll of morbidity, disability and premature mortality, reduce frequent infections known as **exacerbations** of the disease and improve the **quality of life** of patients. In advanced countries such as Greece COPD is due by 90% to **smoking**. The main symptoms of the disease are **cough, sputum expectoration and dyspnea**.

Oxidative stress is a consequence of inability of resident antioxidant mechanisms to neutralize pro-oxidant factors generated endo- or exog-

enously. As a consequence, the oxidants predominate and oxidative stress occurs. Reactive oxygen and nitrogen species (ROS and RNS) are the most prominent products in oxidative stress. Cigarette smoke contains more than 1017 oxidant/free radical molecules per puff and more than 4700 chemicals[1,2].

A variety of oxidants and free radicals provoke an imbalance between oxidants/antioxidants in lung epithelium and systemic circulation of smokers and COPD patients. Thus, therapeutic strategies targeting oxidative stress with pharmacological antioxidant agents or boosting the endogenous levels of antioxidants is likely to be **beneficial as an adjunctive tool** in the treatment of COPD patients[2].

Mucoregulators such as **ambroxol** are used in the treatment of respiratory diseases characterized by impaired **mucus clearance** and have been shown to possess antioxidative activity **in vitro** as well as **in vivo**. This review article focuses on the position of ambroxol as an additional treatment of these diseases. **Ambroxol** [trans-4-(2)amino-3,5-dibromobenzylamino)- cyclohexane hydrochloride] stimulates synthesis and secretion of surfactant by type II pneumocytes and inhibits sodium absorption by airway epithelial cells[3,4].

The **pharmacological effects of ambroxol** cover a wide range, including mucus regulation on gland cells, increased production of pulmonary surfactant, neutralization of oxidative and nitrosative stress, suppression of respiratory virus replication, reduction of proinflammatory cytokines, chemotaxis, respiratory burst of inflammatory cells, tissue lipid peroxidation, and local anaesthetic effects[5-7].

Ambroxol is an active metabolite of bromhexine and has been established for decades in the treatment of acute (e.g. bronchitis) and chronic respiratory diseases (e.g. COPD)[8-10]. Pharmacological and clinical studies showed the **mucoregulative** and **secretagogue** properties of ambroxol[10]. The scientific conclusion of the European Medicines Agency (EMA), on ambroxol has been summarized as relevant for treatment of **bronchopulmonary diseases** thus potentially contributing to the positive benefit-risk profile of the compound[11].

Anti-inflammatory properties of ambroxol on granulocytes and mast cells have been shown in vitro in a mouse model in the context of asthma therapy[12,13]. In two controlled clinical studies ambroxol was used as an **adjuvant in COPD therapy**. In both studies the authors describe positive effects on the prevention or treatment of exacerbations[14,15]. Even though the study design of these trials does not allow to draw safe conclusion (due to the lack of placebo controls), they confirm findings of previous investigations[9,16]. According to The Global Initiative for Chronic Obstructive Lung Disease (GOLD) anti-inflammatory therapy in stable COPD includes mucolytics as they **reduce the risk of exacerbations** in selected populations[17].

A 6-month double-blind, randomized study with 75 mg ambroxol sustained release/day was conducted versus placebo in 214 patients with **chronic bronchitis** in the winter months. 45.5% in the treated group and 14.4% of patients in the placebo group remained exacerbation-free ($p<0.01$). In addition to this highly significant difference, the number of severe exacerbations with fever and the number of sick days ($p<0.01$) differed significantly in favor of the ambroxol-treated group[9]. These results were substantially confirmed by an open-label study including 5,635 patients[18,19]. In the AMETHIST trial in 242 patients with COPD. Patients received long-term treatment with 75 mg ambroxol sustained release b.i.d. for 1 year, or placebo. A total of 38% of placebo-treated patients in a subset of 45 patients with more severe baseline symptoms, were exacerbation-free during the study. In contrast, in the same subgroup, 63% of Ambroxol-treated patients were exacerbation-free ($p=0.038$). The longest lasting study with 75 mg ambroxol sustained release/day was conducted by Ceglain 180 patients with chronic bronchitis present for more than 5 years[16]. This was a randomized, double-blind placebo-controlled study in 22 centers over 2 years. With a small drop-out rate of 13% it was shown that, compared with the placebo group:

- symptoms such as dyspnea, expectoration and cough were markedly reduced,
- lung function parameters such as vital capacity (IVC), forced expiratory volume in 1 second (FEV1) and peak expiratory flow (PEF) were significantly improved,
- there was a reduction in adjuvant medications such as **antibiotics** and **corticosteroids**,

The highly significant reduction in sick days compared with the placebo group is particularly important ($p<0.01$) considering the individual patient's **quality of life**.

Poole and Black[20] pointed out in a systematic analysis conducted for a Cochrane Review that therapy with secretolytic substances is also of socio-economic significance.

Mucoactives are also considered good practice in patients with **bronchiectasis**, a condition characterized by increased mucus production[21].

A pilot study in elderly adults showed effects of ambroxol on the prevention of **acute respiratory infections**,

such as common cold and influenza, compared to an active control (carbocysteine and rebamipide)[22]. A further clinical trial in children with acute pneumonia describes a higher effective rate (sum score of different symptoms) in the group with concomitant ambroxol inhalation, compared to standard care alone[23].

Besides the effect of ambroxol on mucus clearance, further **antiviral**, **antibacterial** and **antifungal** properties have been recently described and published. Different working groups conclude **direct and indirect anti-infectious properties** such as increasing bioavailability of antibiotics by ambroxol[24-35]. Therefore, the available data suggest that the efficacy of ambroxol in COPD and acute bronchitis might at least partly be mediated by these pharmacological properties. It is worth to mention that there is a special interest for ambroxol in the scientific community as an adjuvant in the treatment of infections with **biofilm-producing pathogens** such as Pseudomonas aeruginosa and Candida albicans[24,25,29]. The first studies in animal models provide preliminary evidence for an improved penetration of anti-infectives such as vancomycin and voriconazole in the presence of ambroxol through the biofilm-barriers of these pathogens[30,33] and even a direct inhibition of biofilm formation by ambroxol was shown in a pneumonia rat model[29].

Further studies were published regarding the **prevention of pulmonary complications** in severely ill patients by ambroxol[36-42].

It is worth to mention one trial in lung cancer patients undergoing lobectomy. In this study, short-term perioperative treatment with ambroxol reduced both, the rate of postoperative pulmonary complications and the duration of postoperative hospital stay[37].

A new potential treatment area for ambroxol, as suggested by the rising number of publications in this field, is the treatment of lysosomal storage disorders such as **Morbus Gaucher**[43-50]. In an uncontrolled pilot study, the symptoms of Morbus Gaucher patients did not worsen under ambroxol treatment for 6 months[51]. Further studies are needed to confirm these preliminary findings.

Ambroxol has been available in the EU market since 1978 and is currently used in more than 50 countries worldwide[52,53]. According to a 2008 update report, the **safety** of ambroxol is well-established, since it is based on its use in more than 15,000 patients in more than 100 studies, with a total patient exposure estimated at 4,789,563 patient-years[8]. According to the PRAC 2015 report, the worldwide patient exposure is even higher, estimated to be 31,881,769 patient-years for ambroxol-containing products indicated in secretolytic therapy, but also in the treatment of infant respiratory distress syndrome and in the prophylaxis of postoperative complications.

According to the seven randomized, placebo-controlled trials presented in a latest review[6], ambroxol was well-tolerated during **short-term and long-term treatments** (up to two years), showing no differences with respect to adverse events compared to the placebo groups. This finding falls in line with the results of the 2015 meta-analysis of 34 randomized, placebo controlled clinical trials that compared oral mucolytic therapy versus placebo administered regularly for at least two months in adults with chronic bronchitis or COPD. In a total of 21 studies lasting from 2 to 36 months, 608 adverse events were reported in 3,170 subjects treated with mucolytics versus 669 adverse events in 3,176 placebo-treated subjects, with all adverse events being mild and self-limited (odds ratio, 0.88; 95% confidence interval, 0.78 to 1.00). Hence, this large systematic review of randomized, controlled trials indicates that there is probably no difference between mucolytic and placebo treatments in terms of the total numbers of adverse effects that they cause[54].

In summary, ambroxol is still investigated in both preclinical and clinical trials by research groups worldwide. Recent findings suggest relevant pharmacological and clinical effects particularly in the treatment of infections with biofilm-producing pathogens and the protection from pulmonary complications after surgery or in the intensive care. Further trials are needed to prove the encouraging findings in patients with lysosomal storage disorders.

In conclusion, the multiple effects - secretolytic, secretomotor, mucociliary clearance-promoting, anti-inflammatory and oxidative stress-reducing - of **ambroxol** in combination with the excellent safety profile even in long-term use, raises the interest of its clinical usefulness and drives the need for new studies to elucidate its precise role in the management of chronic respiratory diseases.

AUTHOR CONTRIBUTIONS

CB wrote the manuscript. RN, KM, LS and BP were involved in the data analysis or interpretation of the data and have critically revised the article. All authors have approved the final version of the manuscript. All authors are accountable for accuracy and integrity of the work.

CONFLICTS OF INTEREST

CB is an employee of Sanofi. RN, and BP have received payments for lectures from Sanofi Greece. KM, LS and BP have received payment for advisory boards from Sanofi Greece.

ΠΕΡΙΛΗΨΗ

Αμβροξόλη … περισσότερο από ένα αποχρεμπτικό. Το όφελος της χρήσης της αμβροξόλης σε χρόνιες αναπνευστικές παθήσεις;

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Οι χρόνιες αναπνευστικές παθήσεις περιλαμβάνουν την χρόνια αποφρακτική πνευμονοπάθεια (COPD), το άσθμα, επαγγελματικές πνευμονοπάθειες και βρογχεκτασίες, μεταξύ άλλων. Οι περισσότερες από αυτές τις μακροχρόνιες ασθένειες δεν είναι ιάσιμες και προκαλούν τεράστια οικονομική επιβάρυνση. Τα βλεννορυθμιστικά όπως η αμβροξόλη έχουν χρησιμοποιηθεί εδώ και δεκαετίες ως θεραπεία σε νόσους των πνευμόνων, για να μειώσουν τη βαρύτητα τους και να βελτιώσουν την ποιότητα ζωής, προωθώντας την κάθαρση της βλέννας. Οι επιδράσεις της αμβροξόλης περιλαμβάνουν την αύξηση της παραγωγής του επιφανειοδραστικού παράγοντα, τη μείωση των κυτταροκινών και την εξουδετέρωση του οξειδωτικού στρες στους πνεύμονες. Οι θετικές επιδράσεις της αμβροξόλης έχουν περιγραφεί in vitro και σε κλινικές μελέτες για τη ΧΑΠ, τη χρόνια βρογχίτιδα καθώς και τις οξείες αναπνευστικές λοιμώξεις. Επιπλέον, έχουν περιγραφεί αντιιικές, αντιβακτηριακές και αντιμυκητισιακές ιδιότητες. Η αμβροξόλη έχει καλό προφίλ ασφάλειας. Σε αυτό το σύντομο άρθρο ανασκόπησης περιγράφεται συνοπτικά η τρέχουσα κλινική γνώση όσον αφορά στην αμβροξόλη.

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