More than Expectorant: New Scientific Data on Ambroxol in the Context of the Treatment of Bronchopulmonary Diseases

Abstract

**Background:** Ambroxol has been established for decades in the treatment of acute and chronic respiratory diseases. A reassessment of the benefit-risk was conducted recently.

**Objective:** What new scientific data, relevant for the treatment of bronchopulmonary diseases, were published in the last decade?

**Method:** Systematic literature search via http://www.pubmed.gov with the search term “ambroxol”, covering the publication period from 2006 to 2015. Non-relevant publications were excluded manually.

**Results:** 64 relevant publications could be identified covering both, clinical and preclinical research.

**Conclusion:** The traditional indication of ambroxol as an expectorant is confirmed but new results revealed a better understanding of the various mechanisms of action of ambroxol and the benefits for special patient populations. The available data suggest the use of ambroxol as an adjuvant in anti-infective therapy, particularly in case of infections with biofilm-producing pathogens. Lung-protective properties are discussed in both infants and severely ill adult patients. First results in rare diseases, such as lysosomal storage disorders, show a potential benefit of ambroxol. However, final evidence for the clinical relevance in this special field has yet to be provided.

**Keywords:** Ambroxol; COPD; Bronchitis; Surfactant; Lysosomes; Biofilm

Introduction

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) [1-3]. Pharmacological and clinical studies showed the mucoregulative and secretagogue properties of ambroxol [4]. In 2015 the European Medicine Agency (EMA) reassessed the benefit-risk profile of ambroxol in a PRAC (Pharmacovigilance Risk Assessment Committee) - referral [5,6]. A lately published review revealed new scientific data on ambroxol which can be relevant for treatment of bronchopulmonary diseases thus potentially contributing to the positive benefit-risk profile of the compound [7]. This mini-review intends to summarize these findings accordingly.

A systematic literature research in Medline (pubmed.gov) with the search term “ambroxol” during the publication period from 01.01.2006 until 31.12.2015 was conducted. The search led to 236 hits, of which 64 relevant publications were identified and included. Specific findings are summarized.

Chronic Bronchopulmonary Diseases

Anti-inflammatory properties of ambroxol on granulocytes and mast cells were shown in vitro and in a mouse models in the context of asthma therapy [8,9]. In two controlled clinical investigations ambroxol was used as an adjuvant in COPD therapy. In both publications the authors describe positive effects on the prevention or therapy of exacerbations [10,11]. Though the study designs of these trials do not allow a final conclusion (missing placebo controls), they confirm results of previous investigations [2,12].
Acute Bronchopulmonary Diseases

A pilot study in elderly adults showed effects of ambroxol on the prevention of acute respiratory infections, compared to an active control [13]. 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 [14].

Anti-Infective Properties

Besides the influence of ambroxol on mucus clearance, further antiviral, antibacterial and antifungal properties have recently been described and published. Different working groups conclude direct and indirect anti-infectious properties (such as increasing bioavailability of antibiotics) by ambroxol [15-26]. Therefore, the available database suggests 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 treatment of infections with biofilm-producing pathogens such as Pseudomonas aeruginosa and Candida albicans [15,16,20]. 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 [21,24] and even direct inhibition of biofilm formation by ambroxol was shown in a pneumonia rat model [20].

Lung-Protective Properties

A meta-analysis of randomized controlled trials provides evidence for ambroxol’s protective effect of immature lungs of pre- and new-born infants. The relative risk for a neonatal respiratory distress syndrome under ambroxol therapy was 0.38 compared to control, according to the conclusion of the authors [27]. Further studies were published investigating the prevention of pulmonary complications in severely ill patients by ambroxol [28-34].

Worth to mention is 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 [29].

Rare Diseases

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 [35-42]. In an uncontrolled pilot study, the symptoms of Morbus Gaucher patients did not worsen under ambroxol treatment for 6 months [43]. Further studies are needed to confirm these preliminary findings.

Conclusion

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 treatment of infections with biofilm-producing pathogens and the protection from pulmonary complications after surgery or in intensive care. Further trials are needed to prove the encouraging finding in patients with lysosomal storage disorders.

References
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