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The use of ambroxol in various fields of medicine outside medical indications - A Review of the Current Literature

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Abstract

Introduction: Ambroxol is a drug that has a multifaceted application in medicine. Its main effects are mucolytic, mucokinetic, anti-inflammatory, antioxidant and local anesthetic. Ambroxol is used in various fields of medicine, including in the treatment of respiratory diseases, supporting the production of surfactant, treating sore throat and neuropathic pain. Ambroxol has been identified as a component that enhances the enzymatic activity of mutated glucocerebrosidase resulting from various mutations resulting from misfolding mutations in the GBA gene [1]. Experimental studies are also underway on the treatment of neurodegenerative diseases such as Parkinson's disease, amyotrophic lateral sclerosis as well as in the treatment of stroke and inhibition of Clostridioides difficile toxins TcdA and TcdB. This article highlights the variety of applications of ambroxol, which was initially used only in respiratory diseases.

Study Objective: The aim of this article is to comprehensively review the literature on the use of ambroxol in various fields of medicine in order to expand the research and use of ambroxol in diseases beyond its registered indications.

Materials and Methods: Electronic database including PubMed, science networks, Google Scholar, to identify studies and literature reviews on the use of ambroxol in various fields of medicine.

State of the Art: This review examines the use of ambroxol beyond its medical indications, mainly emphasizing its use in neuropathic pain, Parkinson's disease, amyotrophic lateral sclerosis, Gaucher's disease. Attention is also paid to its use in stroke patients and in the inhibition of Clostridioides difficile toxins TcdA and TcdB.

Conclusion: Ambroxol is an antitussive drug that has been used for years. More and more studies are available on the use of ambroxol beyond its medical indications, which show the validity of the concept of its use in other fields of medicine than respiratory diseases.

Keywords: “ambroxol”, “mucolytic”, “neuropathic pain”, “Parkinson’s disease”, “amyotrophic lateral sclerosis”, “Gaucher’s disease”, “stroke”, “Clostridioides difficile TcdA and TcdB.”

1. INTRODUCTION:

Ambroxol (2-amino-3,5-dibromo-N-[trans-4-hydroxycyclohexyl] benzylamine) is a metabolite of bromhexine, a well-known drug used for years primarily in the treatment of respiratory diseases. It also works well in relieving sore throat [2], but this substance is not used as an analgesic despite the fact that there are studies conducted on animals indicating the suppression of pain-related behaviors, even in situations of chronic pain [3,4,5]. Its mechanism of action affects the ability to increase the secretion of mucus in the respiratory tract, reduce its viscosity and stimulate the activity of cilia, which facilitates the removal of secretions6. In addition to its mucoactive effects, it also has secretolytic, anti-inflammatory, antioxidant, and local anesthetic effects, as well as surfactant-stimulating effects. [7,6,8]

2. OBJECTIVE OF THE STUDY:

The aim of this work is to present the therapeutic benefits of ambroxol in diseases and pathological conditions that go beyond its traditional use as a mucolytic drug. The studies concern the effects of ambroxol such as its ability to modulate the activity of enzymes such as glucocerebrosidase, its neuroprotective properties and its impact on neurodegenerative processes, neuromuscular functioning and its effect on GCase growth. In addition, the article

draws attention to the effect of ambroxol on the generation and propagation of pain signals as well as the nature of ambroxol's effects on neuronal survival by moderating microglial activity.

3. MATERIALS AND METHODS:

Electronic databases including PubMEd, Scopus Web of Science and Google Scholar were searched to find studies and literature reviews on the use of ambroxol outside the registered indication. The review included studies that were published between 2004 and 2024. These studies concerned the use of ambroxol in the treatment of neuropathic pain, Gaucher's disease, Parkinson's disease, amyotrophic lateral sclerosis, stroke, inhibition of Clostrdioides difficile toxins TcdA and TcdB. Studies with limited sample size, studies without full text available online, and articles not subject to peer review were excluded.

4. STATE OF KNOWLEDGE:

4.1. Treatment of neuropathic pain

Ambroxol affects the function of voltage-gated sodium channels, especially Nav1.8 channels, which have a key function in generating and propagating the pain signal [9,10]. Inhibiting these channels with ambroxol can reduce the excitability of nociceptive neurons and suppress the transmission of neuropathic pain [11]. The first observations on the use of ambroxol in neuropathic pain were reported by Kern and Weiser in 2015 [12]. The authors presented 7 patients with refractory peripheral neuropathic pain who responded to local treatment with ambroxol (20% cream: 10 g ambroxol, 5 g DMSO, supplemented to 50 g Linola cream). Ambroxol treatment was an addition to basic treatment, i.e. lidocaine or capsaicin patches. All of them experienced a reduction in pain from 2 to 8 on a numerical scale and the effect lasted from 3 to 81 hours after application of the cream. No side effects were reported with the use of ambroxol cream [2,12]. These studies show that the use of low doses of topical ambroxol relieves neuropathic pain.

In studies in 5 patients with trigeminal neuralgia, a 20% topical ambroxol cream was used in addition to the basic treatment [13]. All patients reported a reduction in pain from 2 to 8 in the numerical scale [13]. Pain relief was noted after 15-30 minutes and lasted from 4-6 hours [13]. This effect was most likely due to the blocking of sodium channels, which are abundant in peripheral trigeminal neurons. The expression of these channels is increased in trigeminal neuralgia.

In a 2010 study by Ham et al., the analgesic effects of ambroxol were examined in rats with neuropathic pain following spinal cord injury [4]. Neuropathic pain following spinal cord injury is caused by skin hypersensitivity and spontaneous pain that may be below the level of

injury. Ambroxol was administered to rats with spinal cord injury at the midthoracic level. Injured rats, severe thermal and mechanical hypersensitivity was observed in the hind paws. After oral administration of ambroxol, a significant decrease in mechanical hypersensitivity was achieved at a dose of 1000 mg/kg. This effect was seen 30 minutes after administration and lasted for 3 hours. At a dose of 100 mg/kg, partial reversal of thermal hypersensitivity was seen. In this case, the analgesic effect lasted for two hours. The differential dose response may be due to the low expression of Nav 1.8 in large-diameter mechanically sensitive afferent fibers and the high expression of small-diameter thermal nociceptors. Intrathecal administration of ambroxol at a dose of 300 μg did not affect the symptoms of neuropathic pain [4].

No serious adverse events or skin reactions have been observed in the treatment of neuropathic pain with ambroxol [4,13]. Ambroxol treatment for neuropathic pain is an emerging field of research, and further studies are needed on the effect, dosage, and safety of combining it with other analgesics.

This drug has gained much attention due to its use in the treatment of neuropathic pain, ischemic stroke, Parkinson's disease, amyotrophic lateral sclerosis, Gaucher's disease, and inhibition of Clostridoides difficile toxins TcdA and TcdB.

The multidirectional action of ambroxol, which is supported by numerous scientific studies, plays a key role in modern pulmonology and beyond. This article aims to present the wide application of ambroxol in medicine.

4.2. Gaucher disease

Gaucher disease (GD) is a congenital lysosomal storage disease caused by a mutation in the GBA1 gene, which causes insufficient activity of the lysosomal enzyme glucocerebrosidase and deposition of glucocerebroside in various tissues [14,15,16]. In 2009, studies showed that ambroxol acts as a pharmacological chaperone for mutated GCase when taken in high doses [17]. By binding to misfolded GCase, ambroxol facilitates its correct folding and recovery of function [17,18]. Ambroxol has been used off-label and several reports have been published on this subject. In studies of a patient with neuronopathic Gaucher disease, who was given high doses of oral ambroxol as part of the basic therapy, a reduction in pain was observed [19,20,21]. Long-term treatment with ambroxol was safe and improved the patient's condition. The improvement in the patient's condition was more visible in people who started treatment at a younger age and whose symptoms were milder [18].

Another case is a 38-year-old patient with GD type 3, reporting constant pain in the sacrolumbar spine, without any pathology visible in imaging studies. When taking painkillers, i.e. paracetamol, tramadol, the pain was partially controlled. Ambroxol was used in the

treatment at a dose of 150 mg/d, but without any effects. After introducing ambroxol at a dose of up to 450 mg/d, the intensity of the pain decreased, and in the following months the pain subsided. In further studies, the dose of ambroxol was reduced, which caused a return of pain within a week, but the pain disappeared after reintroduction of a higher dose [22].

In the study conducted by Narita et al., the effect of ambroxol administration in combination with enzyme replacement therapy was examined in 5 patients with neuropathic Gaucher disease. The efficacy of the therapy was checked on the basis of glucocerebrosidase activity in lymphocytes and glucosylsphingosine level in cerebrospinal fluid. The patients were given ambroxol initially 3 mg/kg (in patients 1,2,3) and 9 mg/kg (in patient 4), gradually increasing to a target dose of 25 mg/kg/day or a maximum dose of 1300 mg/day. In patient 5, the dose of 25 mg/kg was administered from the beginning [19]. The results of the studies were satisfactory. High doses of ambroxol caused a significant increase in lymphocyte glucocerebrosidase, blood-brain barrier penetration, and a decrease in cerebrospinal fluid glucosylsphingosine levels. All patients showed a decrease in myoclonus, seizure frequency, and improved pupillary light response. The decrease in myoclonus led to an improvement in motor function in patients, which allowed them to walk again [19]. This study highlights the importance of using ambroxol in patients with neurological symptoms and improving the quality of life of these patients and their families.

No significant adverse events were noted in the cited studies. Most adverse events were mild and transient, including nausea, salivation, diarrhea, and rash [18,19]. Hence, there is evidence that long-term use of ambroxol is safe.

Ambroxol may be a therapeutic option when ERT or SRT drugs are not available or when they are too expensive for the patient. However, little is known about the long-term effects of ambroxol use in high doses, and further research is needed to determine the risks and benefits.

4.3. Parkinson's disease

Parkinson's disease is associated with the deposition of the protein α-synuclein in subcortical and cortical areas of the brain [23, 24]. One of the risk factors for Parkinson's disease (PD) is the carriage of the β-glucosidase gene (GCase; gene name GBA1). Studies have shown that increasing the level of GCase reduces the level of α-synuclein. Abroxol is a chaperone for GCase, so it can increase the level of GCase and thus reduce the level of α-synuclein [25, 26, 27,28]. In addition, GCase activity is reduced in the cerebrospinal fluid of Parkinson's disease patients with and without the GBA1 mutation compared to the control group [28]. Thus, ambroxol may be a drug that will modify the course of Parkinson's disease [29].

In 2020, studies were published on the efficacy of ambroxol in Parkinson's disease and Gaucher disease. The study included 24 patients, but was completed by 18 patients with PD, including 8 patients with GBA-PD [30]. Ambroxol levels were undetectable in the initial CSF and blood tests. Patients were given ambroxol, increasing the dose to a maximum of 1260 mg for 6 months. After 186 days, the ambroxol level in the CSF was 156 ng/ml. The CSF was assessed in 17 patients, one patient was excluded due to contamination of the CSF with red blood cells. An increase in the concentration of GCase and α-synuclein in the CSF was noted. The overall increase in CSF α-synuclein, which was noted in previous studies, indicates the effect of ambroxol on α-synuclein metabolism [25,31,32,33]. The increased expression of the CFR GCase protein indicates the effect of ambroxol on the GCase pathway. No serious adverse events were observed, and an improvement in the manifestation of PD symptoms was observed [30].

In 2021, studies were conducted on a group of 41 patients who were given high-dose ambroxol. All patients with GD3 received ambroxol as an adjunct to ERT, and six patients with GD1 and GBA PD as a single therapy. The results of the studies provide satisfactory results. In patients, among others, a reduction in epileptic seizures in terms of number and intensity, a reduction in myoclonic seizures were noted. The adverse events were mostly mild or transient. To reduce the number of side effects, it has been suggested to gradually increase the dose of ambroxol, every few days or every week, until a maximum dose of 25 mg/kg is reached [34].

In many countries, high doses of ambroxol have been started in patients with GD or GD1, PD associated with GBA, and GBA carriers with PD and/or dementia. Clinical trials are very time-consuming and would take a long time to complete, so ambroxol has been used off-label in high doses as an adjunct to ERT or in patients who have not been previously treated and do not have access to ERT [34].

Many physicians, especially in developed countries, do not recommend the use of ambroxol in Parkinson's disease because the drug is off-label and they have concerns about its safety.

4.4. Amyotrophic Lateral Sclerosis

Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disease that results in the gradual loss of motor neurons located in the cerebral cortex and spinal cord, located in the brain stem and spinal cord. This process leads to muscle denervation. ALS causes progressive symptoms such as paralysis, muscle atrophy, muscle tremors (fasciculations), and spasticity and affects the central nervous system and peripheral organs (Schmitt et al., 2014). Growing evidence links sphingolipid metabolism to the pathophysiology of ALS. In both animal models

and humans, levels of ceramides, glycosylceramides, and gangliosides are dysregulated in the central nervous system and at the neuromuscular junction. Glucosyceramide acts as the major precursor of glycosphingolipids, which are degraded by lysosomal glucocerebrosidase (GBA1) or nonlysosomal glucocerebrosidase (GBA2). GBA2 is markedly increased in SOD1 ^{G86R} mice, a familial animal model of ALS, even before the onset of disease. The study examined the effect of ambroxol, which is a GBA2 inhibitor in SOD1 ^{G86R} mice [35]. In the symptomatic stage of the disease, GBA1 in SOD1 ^{G86R} models compared to control models was not significantly changed, whereas GBA2 in SOD1 ^{G86R} mice was significantly increased in the spinal cord at day 105. An increase in GBA2 was also noticeable in asymptomatic mice. A 2009 study confirmed that ambroxol inhibits GBA2 activity [19]. Asymptomatic SOD1 ^{G86R} mice were administered ambroxol from day 75 to day 95 to confirm that the drug delays the onset of ALS and preserves the integrity of motor units, thereby increasing the survival of SOD1 ^{G86R} mice. Body weight and muscle strength of mice were measured every other day. The number of motor neurons in the lumbar spinal cord was significantly higher in SOD1 ^{G86R} mice treated with ambroxol, indicating that presymptomatic use of ambroxol slows neurodegeneration. ABX significantly protects muscle innervation in SOD1 ^{G86R} mice, as they showed twice as many neuromuscular connections as the group receiving the drug from day 95. Body weight loss was also smaller after ABX administration, and SOD1 ^{G86R} mice were heavier. Studies have shown that GBA2 activity is elevated in SOD1 ^{G86R} mice already in the presymptomatic stage of the disease, and ambroxol can inhibit its activity. Later administration of ABX at the beginning of the disease also slows disease progression and prolongs survival [35]. In summary, the results of the studies indicate that ambroxol has an effect on improving muscle strength and delaying the onset of the disease.

4.5. Stroke

A stroke is a sudden life-threatening condition that manifests itself with focal or generalized brain dysfunctions that last longer than 24 hours and require absolute hospitalization (WHO definition). Studies conducted so far in mice and humans have shown therapeutic concentrations of ambroxol in the brain [30,36]. The conducted studies hypothesized that direct administration of ambroxol after stroke may directly affect the rescue of neurons if used immediately after stroke. In 2023, studies were conducted on 53 rats in which magnetic resonance imaging was performed to examine stroke volume, edema, white matter integrity, MRI image in the resting state and one month after the occurrence of ischemic stroke. In a comparison of control animals with animals that received ambroxol, significantly higher vasogenic edema occurred in the control group in the acute phase. In the T2 MRI phase, the

signal was significantly reduced in stroke lesions in animals administered ambroxol after one month compared to the control group, which indicates a reduction in the areas of liquid necrosis. In patients with reduced stroke volume, better behavioral results were observed as well as changes in structural and functional connectivity, and most importantly, after one month of ambroxol administration in the chronic phase of stroke, less degeneration of the white matter of the external capsule was demonstrated compared to animals not taking ambroxol [37].

To sum up, the results of the studies can be stated that ambroxol supports energy metabolism, cellular homeostasis, membrane repair mechanisms and redox balance.

Other studies have shown that ambroxol effectively penetrates the blood-brain barrier (BBB) and has no harmful effects even in high doses [23,30,38]. Microglia play a protective role in the brain, they are seen as the first non-neuronal cells that respond to acute brain injuries, including, among others, intracranial hemorrhage (ICH) [39,40]. Evidence has shown that activated microglia are a source of chemokines, cytokines, prostaglandins, proteases, and other immunomodulatory molecules in the brain [40]. A study conducted in 2020 examined the effect of ambroxol on functional recovery in mice with ICH. Intraperitoneal administration of 35 mg/kg or 70 mg/kg ambroxol immediately and 24 hours after ICH and for 2 consecutive days once daily supported neuronal survival and reduced white matter bundle damage by attenuating microglial activity and decreasing proinflammatory cytokines in mice with ICH. Ambroxol had a beneficial effect on improving brain function and decreasing brain water content and cellular edema after ICH [41].

4.6. Inhibition of Clostrodioides difficile toxins TcdA and TcdB

Recent studies have shown the effect of ambroxol on preventing acidification of cellular organelles, therefore, studies were also conducted on the effect of ambroxol on the cytotoxic effects of TcdA and TcdB. The transfer of exotoxins from endosomal vesicles to the cytosol requires acidification of endosomes. Ambroxol significantly reduced the morphological changes caused by these toxins. What is particularly surprising about the effect of ambroxol is that, regardless of the effect on endosomal acidification, it caused a decrease in intracellular toxin activity. This drug protected cells from TcdA and/or TcdB by directly inhibiting glucosyltransferase activity. In the quantitative analysis of ambroxol treatment, a protective 6-hour effect of the drug on the morphology of cells exposed to toxins was noted. At the same time, studies attempted to inhibit C2 toxin, but without success. One possible hypothesis for why C2 toxin was not inhibited is that the pH of the endosome is still sufficiently acidic for C2 toxin to deliver its enzyme subunit c2l to the cytosol [42]. These studies confirmed the effect

of ambroxol as an inhibitor of TcdA and TcdB toxins. Ambroxol has potential as a therapeutic agent for CDAD.

5. CONCLUSIONS:

Ambroxol is a drug that, in addition to its registered mucolytic, mucokinetic, anti-inflammatory, antioxidant and local anesthetic effects, also has other properties. Its main action is to thin mucus and facilitate its removal from the respiratory tract. However, in recent years, studies have shown that ambroxol can be used outside of its official indications.

The main mechanisms of action of ambroxol outside of its indications are:

- Inhibition of voltage-gated sodium channels reduces the excitability of nociceptive neurons, which in effect suppresses the transmission of neuropathic pain.
- Binding to mutated GCase acts as a chaperone, allowing it to fold correctly and regain its function, which is used in Gaucher disease
- Elevating GCase levels reduces the level of α-synuclein, which accumulates in subcortical and cortical brain areas in Parkinson's disease, which is why it can be used in the treatment of this disease
- Immediate administration after a stroke can affect the survival of neurons and reduce damage to white matter fiber bundles by reducing microglial activity and pro-inflammatory cytokines, positively affecting the improvement of brain function.
- By neutralizing TcdA and/or TcdB toxins, it is a candidate for further studies on supporting C. difficile therapy.
- Being an inhibitor of GBA2, which is increased in individuals with amyotrophic lateral sclerosis, it slows down the course of the disease and prolongs survival time.

Despite the fact that ambroxol is an inexpensive drug and easily available without a prescription, it is still not readily used due to the lack of registration in the above diseases. In some countries, especially the poorest ones, a large number of people still cannot afford this drug because it is not reimbursed. In many countries, ambroxol is not available, even as a cough medicine. Many doctors are reluctant to recommend an unregistered drug, which is why there are doubts about the effectiveness and safety of using ambroxol outside of its registered indications.

DISCLOSURES

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