

O.K. Duda, V.O. Boyko, L.P. Kotsiubailo, A.I. Konoplianiuk

Shupyk National Medical Academy of Postgraduate Education, Kyiv, Ukraine

Ambroxol in comprehensive treatment of patients with acute respiratory diseases

Abstract. The article presents data on optimization of pathogenetic therapy in patients with acute respiratory diseases with manifestations of tracheitis, bronchitis and complicated by community-acquired pneumonia in adults. The etiological structure of acute respiratory diseases and resistance to antibacterial preparations are described. The role of ambroxol hydrochloride in comprehensive treatment of patients with acute respiratory diseases with various complications from the respiratory system is shown. It has been established that the use of ambroxol hydrochloride positively affects the basic etiological process, reduces the time of hospital stay due to the rapid termination of bacterial excretion by the average of 3.8 ± 0.7 days in 75 % of patients ($p = 0.001$).

Keywords: ambroxol hydrochloride; acute respiratory diseases; productive cough; treatment; adults

Introduction

Acute respiratory diseases (ARDs) are the most common infectious diseases affecting all age groups. Among causes of temporary disability, they occupy the first place — even in the mid-epidemic period, they affect 1/6th of the population of the planet. In Ukraine annually 10–14 million people suffer from ARDs, which accounts for 25–30 % of all and about 75–90 % of infectious diseases in Ukraine [1]. WHO experts note that, in recent years, this the most widespread infectious group among human population has a steady tendency to increase. Social causes associated with the global process of ever-increasing urbanization, closer contacts of people practically anywhere in the world and the strengthening of intercontinental migration processes will contribute to the further spread of ARDs [1, 2].

The epidemic process in ARDs caused by non-viral pathogens is much more complicated due to not so much etiological diversity, but the different levels of contagiousness, less susceptibility of a person, the possibility of preservation of pathogens not only in the human population, but also among animals [3].

The real lack of the possibility of using specific diagnostic methods for etiological decryption in each case of the disease does not reveal the true level of prevalence of both ARVI and ARD of another etiology (legionellosis, mycoplasma, coccus, rickettsia, etc) [4]. The prevalence

of these diseases on the globe, the involvement of a large number of people in the epidemic process, sometimes severe respiratory diseases for humankind.

In adults, ARDs are most often caused by such bacterial microorganisms see Fig. 1.

They cause the appearance of various clinical manifestations — nasopharyngitis, quinsy (acute tonsillitis), bronchitis. Pathogens of this group are more frequent than the viruses, causing the development of pneumonia. In the pathogenesis of some of them (mycoplasmosis, chlamydia, rickettsiosis), cellular immunity is of great significance, and its certain disadvantages often lead to the persistence of these pathogens. Therefore, in many cases, we are not dealing with another infection, but with the reactivation of persistent infection, which must be considered in the treatment [5, 6].

Cough is one of the frequent and main signs of respiratory diseases. The reason for coughing can be direct irritation of sensitive endings (receptors) of the mucous membrane of the respiratory tract (RT) — pharynx, larynx, trachea, bronchi. There is less observed cough of reflex origin, when the source of irritation is outside the RT. Cough is a complex reflex that has afferent paths from the cough receptors for sensitive endings of the trigeminal, jaundice, upper larynx and vagus nerves to the “cough center” in the brain stem, and the efferent link of the reflex, including the rotary, laryngeal and spinal cord (C1 and C4) nerves [7].

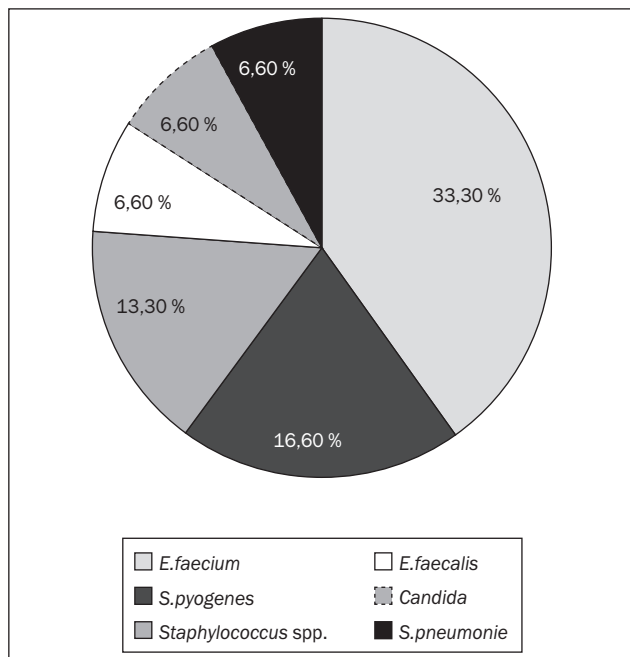


Figure 1. Share of various pathogens in the structure of patients with ARDs (O.K. Duda, L.P. Kotsiubailo, 2015)

According to the duration, cough can be acute (up to 3 weeks), subacute (prolonged) — more than 3 weeks and chronic (from 3 months and more). Attack-like (at pertussis), periodic (at bronchitis), continuous, short (at pleurisy). According to the timbre, cough can be barking (at lesion of larynx), swollen or silent in the case of inflamed and ulcerous vocal cords. Depending on the presence of sputum, cough can be productive (with sputum evacuation) and non-productive. Cough with sputum evacuation may be due to bronchitis, bronchiectasis, inflammation of the lungs, tuberculosis of the lungs. Non-productive cough often occurs with diseases of the upper respiratory tract (URT), compression of the bronchi by a foreign body and in the initial stages of inflammatory diseases of the bronchi and lungs [8, 9].

Given that cough is one of the manifestations, often the only one, of any disease or pathological condition, attempts to eliminate this symptom without explaining its cause are certainly false. When establishing the nature of cough, first of all, it is necessary to conduct etiologic or pathogenetic treatment of the underlying disease [10].

In the vast majority of bronchopulmonary diseases, an improvement in the “drainage” function of the bronchial tract, including the use of pharmacological agents, is required. Recently, new drugs have appeared which allow to change rheological properties of sputum and indicators of adhesion, as a consequence — to facilitate the removal of sputum by a physiological way [11].

Comprehensive treatment of patients with ARDs with manifestations of lesion of the upper and lower respiratory tracts (URT, LRT) along with pathogenetic therapy should include drugs that reduce the viscosity

and elasticity of sputum and have an effect on the local immunity of the RT.

Preparations used to facilitate sputum evacuation are divided into 2 main groups:

- stimulate expiration (secret engine);
- mucolytic (bronchosecretolytic).

Today, among known mucolytics, for more than 30 years, ambroxol has one of the leading places in the complex treatment of respiratory diseases of various etiologies, is popular and has serious recommendations [12, 13]. The active substance of the drug is ambroxol hydrochloride. It thins sputum due to stimulation of the glands of serous mucosal cells of the bronchi, normalizes the ratio of serous and mucous components of sputum, stimulates the production of enzymes that cleave the bonds between mucopolysaccharides in sputum, stimulates the formation of surfactant, which also normalizes the rheological parameters of sputum, decreasing its viscosity and adhesion properties [6, 10, 11]. It directly stimulates the movement of cilia and prevents them from sticking together, contributing to the evacuation of sputum. The drug has a small analgesic effect, which is of great importance in the treatment of a variety of pathologies, which undesirably stimulate the cough reflex [12].

In addition to the main mucolytic effect, special attention has always been given to the additional effects of ambroxol. In the review by K. Beeh et al., there is summed up information on the most prominent anti-inflammatory properties of ambroxol, such as inhibition of oxidative stress, enhancement of local protective mechanisms, reduction of proinflammatory cytokines and metabolites of arachidonic acid, chemotaxis of inflammatory cells and peroxidation of lipids in tissues [13].

An important property of ambroxol is its ability to interfere with the formation of biofilms of bacteria. M. Cataralis et al. noted the additional anti-inflammatory property of the ambroxol molecule by inhibiting the activity of neutrophils at many levels, thereby improving the mucociliary clearance [14].

M. Malerba and V. Ragnoli have reported data from studies confirming that the ambroxol molecule possesses additional secretolytic, anti-inflammatory and antioxidant activity, causing a local anesthetic effect [10, 13].

It is proved that ambroxol is able to increase the amount of surfactant, increasing its synthesis and inhibiting its degradation in type II alveolocytes. An evaluation of the effectiveness and safety of the use of ambroxol drugs as a preventive therapy for the development of respiratory distress syndrome in preterm infants was performed. In 12 clinical trials, 1,335 premature infants were studied. The respiratory distress syndrome was significantly lower in the 1st group of children receiving ambroxol compared to the 2nd group of patients receiving placebo or corticosteroids. In the 1st group of children, the risk of developing the infection was lower [12–14]. It has been shown that ambroxol stimulates the synthesis of endogenous surfactant and promotes

its release into the lumen of the alveoli and bronchi, which, in turn, leads to the normalization of impaired processes of production and transport of sputum [10]. In clinical practice, it leads to the restoration of the function of the mucous membrane of the respiratory tract, increases the fluidity of sputum [11, 12]. This makes it possible to wide use this drug in patients with acute respiratory diseases with manifestations of acute respiratory distress syndrome.

Ambroxol enhances local immunity by activating tissue macrophages and increasing the production of secretory IgA, and mainly stimulates the production of mononuclear inflammatory mediators (interleukin-1 and tumor necrosis factor), reinforces the natural protection of the lungs by activating macrophages. The ability to inhibit the release of inflammatory factors on immune cells lack provoking bronchospasm and immunomodulatory effect of ambroxol has advantages in choosing a drug for comprehensive treatment of patients with ARDs and symptoms of bronchospasm and wheezing including pregnant women and newborns [12].

Ambroxol does not contain sugar and alcohol, therefore, unlike other mucolytic drugs, it can be used in patients with diabetes mellitus or with impaired glucose tolerance.

It should be noted that ambroxol potentiates the action of antibacterial drugs. To date, a number of papers have been published in which the interaction of ambroxol with antibiotics was studied. The experimental data showed that the average concentration of ampicillin, erythromycin and amoxicillin in the lungs of rats treated with antibiotic + ambroxol, were by 23 and 27 % respectively higher than in rats that received only antibiotic. Differences in all cases were statistically significant ($p < 0.05$). A similar effect was found in relation to other (β -lactam antibiotics including second and third generation cephalosporins, as well as second generation fluoroquinolones (ciprofloxacin and ofloxacin)). This effect is noted both in oral and parenteral administration of antibiotics. A reliable explanation of the mechanism of this phenomenon has not yet been found [13, 14].

Conclusions

Ambroxol has a special place in the complex treatment of patients with ARDs with the development of URT and LRT, manifested by the symptom of cough (non-productive or productive), as it is used to potentiate the action of antibiotics, prevent the development of acute respiratory distress syndrome, including preterm infants.

Since ambroxol hydrochloride is compatible with virtually all medications that are used in the treatment of ARDs and therefore it is recommended for wide use in patients with various bronchopulmonary diseases, including pregnant women.

Today ambroxol hydrochloride is considered a "classic" mucolytic and serves as a benchmark for the evaluation of the effectiveness of new combined medications in the treatment of patients with ARDs.

Conflicts of interests. Authors declare the absence of any conflicts of interests that might be construed to influence the results or interpretation of their manuscript.

References

1. *Unified clinical protocol for primary care for adults and children. Acute respiratory infections. Order of the Ministry of Health of Ukraine. July 16, 2014, № 499.*
2. Kramarev S.O. *Approaches to antibacterial therapy of acute respiratory infections in children / Kramarev S.O., Yevtushenko V.V. // Actual infectology. — 2015. — № 1(6). — P. 7-12.*
3. Feshchenko Yu.I. *Pneumonia today: clinical variants, etiology and etiotropic therapy / Yu.I. Feshchenko // Treatment and diagnostics. — 2000. — № 2. — P. 18-24.*
4. Simonova O.I., Gorinova Yu.V. *Inhalation therapy with ambroxol solution (Lazolvan®): benefits, application specifics, effectiveness // RMJ. — 2014. — № 21. — P. 1530.*
5. Simonova O.I. *Clinical effects of ambroxol hydrochloride (lasolvan®): what does the effectiveness of the drug depend on? // Pediatrics. — 2011. — № 5. — P. 128-133.*
6. Beeh K.M., Beier J., Esperester A., Paul L.D. *Antiinflammatory properties of ambroxol // Eur. J. Med. Res. — 2008. — Vol. 13(12). — P. 557-562.*
7. Cataldi M., Sblendorio V., Leo A., Piazza O. *Biofilm-dependent airway infections: A role for ambroxol? // Pulm. Pharmacol. Ther. — 2014. — Vol. 28 (2). — P. 98-108.*
8. Malerba M., Ragnoli B. *Ambroxol in the 21st Century: Pharmaceutical and clinical update // Expert Opin. Drug Metab. Toxicol. — 2008. — Vol. 4(8). — P. 1119-1129.*
9. Huang J., Xu J., Tian L., Zhong L. *A thioredoxin reductase and / or thioredoxin system-based mechanism for antioxidant effects of ambroxol // Biochimie. — 2014. — Vol. 97. — P. 92-103.*
10. Zhang Z.Q., Wu Q.Q., Huang X.M., Lu H. *Prevention of respiratory distress syndrome in preterm infants by antenatal ambroxol: a meta-analysis of randomized controlled trials // Am. J. Perinatol. — 2013. — Vol. 30(7). — P. 529-536.*
11. Cunningham F.M. et al. *Effect of Ambroxol on mucociliary transport in the guinea pig // Br. J. Pharmacol. — 1983. — Vol. 80 (Suppl). — P. 693.*
12. Eckert H., Lux M., Lachmann B. *The role of alveolar macrophages in surfactant turnover. An experimental study on metabolite VIII of bromhexine (ambroxol) // Lung. — 1983. — Vol. 161. — P. 213-218.*
13. Heath M.F., Jacobson W. *The action of lung lysosomal phospholipases is dipalmitoyl phosphatidylcholine and its significance for the synthesis of pulmonary surfactant // Pediatr. Res. — 1980. — Vol. 14. — P. 254-258.*
14. Bonnetti P. *Ambroxol plus amoxicillin versus amoxicillin alone in various respiratory tract infections. Investig // Medica Internacional. — 1993. — Vol. 20. — P. 99-103.*

Received 18.10.2017 ■

Дуда О.К., Бойко В.О., Коцюбайло Л.П., Конопляник А.І.

Національна медична академія післядипломної освіти ім. П.Л. Шупика, м. Київ, Україна

Амброксол у комплексному лікуванні хворих із гострими респіраторними захворюваннями

Резюме. У статті описано інноваційні дані щодо оптимізації патогенетичної терапії в пацієнтів із гострими респіраторними захворюваннями з проявами трахеїту, бронхіту, ускладненими пневмонією в дорослих. Описано етіологічну структуру гострих респіраторних захворювань та стійкість до антибактеріальних препаратів. Показана роль амброксолу гідрохлориду в комплексному лікуванні хворих із гострими респіраторними захворюваннями з різними ускладненнями

з боку дихальної системи. Встановлено, що використання амброксолу гідрохлориду позитивно впливає на основний етіологічний процес, зменшує термін стаціонарної стадії лікування через швидке припинення бактеріальної екскреції в середньому на $3,8 \pm 0,7$ дня у 75 % пацієнтів ($p = 0,001$).

Ключові слова: амброксолу гідрохлорид; гострі респіраторні захворювання; продуктивний кашель; лікування; дорослі

Дуда А.К., Бойко В.А., Коцюбайло Л.П., Конопляник А.І.

Национальная академия последипломного образования им. П.Л. Шупика, г. Киев, Украина

Амброксол в комплексном лечении больных с острыми респираторными заболеваниями

Резюме. В статье описаны инновационные данные об оптимизации патогенетической терапии у пациентов с острыми респираторными заболеваниями с проявлениями трахеита, бронхита, осложненными внебольничной пневмонией у взрослых. Описаны этиологическая структура острых респираторных заболеваний и устойчивость к антибактериальным препаратам. Показана роль амброксола гидрохлорида в комплексном лечении пациентов с острыми респираторными заболеваниями с различными осложне-

ниями со стороны дыхательной системы. Установлено, что использование амброксола гидрохлорида положительно влияет на основной этиологический процесс, уменьшает продолжительность стационарной стадии лечения из-за быстрого прекращения бактериальной экскреции в среднем на $3,8 \pm 0,7$ дня у 75 % пациентов ($p = 0,001$).

Ключевые слова: амброксола гидрохлорид; острые респираторные заболевания; продуктивный кашель; лечение; взрослые