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# Berodual<sup>®</sup> in the treatment of bronchial asthma

**Key words:** *bronchial asthma, Berodual.*

Bronchial asthma (BA) – is a chronic disease caused by increased sensitivity of the bronchi to various kinds of stimulation. BA manifests itself by attacks caused by bronchial obstruction and stop autonomously or as a result of treatment. BA occurs with alternating exacerbations and remissions. During remission the disease may not manifest. Exacerbation is usually short and lasts from a few minutes to several hours, after that the patient's condition is fully normalized. However, there are long-term exacerbations when attacks of varying severity are repeated daily. In severe cases of bronchial obstruction it is hardly possible to take it under control within a few days or even weeks. This condition is known as status asthmaticus [1, 2].

Recently, doctors increasingly face asthma. In developed countries, about 5 % of the adult population and about 10 % of children suffer from this disease. The disease can occur at any age, but mostly in childhood: approximately in half of the patients asthma manifests up to 10 years of age, yet a third – up to 40. Boys suffer asthma two fold more than girls. But the sex ratio equalizes till 30 years of age. Bronchial asthma is a multifactorial disease, which is based on genetic predisposition and exposure to aggressive environmental factors. Accumulation of new data on the pathogenetic mechanisms of BA to the early 1990s required the revision of our views on this disease. According to modern concepts a chronic airway inflammation underlies the pathogenesis of asthma; many cells and cellular elements, particularly mast cells, eosinophils, T-lymphocytes, neutrophils and epithelial cells play a role in its development [3, 4]. If there is a predisposition, inflammation leads to recurrent episodes of wheezing, dyspnea, heaviness in the chest and coughing, particularly at night and / or early morning. These symptoms are usually accompanied by widespread but variable bronchial obstruction, which is almost always reversible completely

spontaneously or under the influence of treatment. Inflammation leads to the formation of increased airway sensitivity to a variety of stimuli, which usually cause no reaction in healthy individuals. This is called “bronchial hyper reactivity”, which may be specific and nonspecific. Specific hyper reactivity is a bronchial hypersensitivity to certain specific allergens that have caused the development of asthma. Nonspecific hyper reactivity is sensitivity to various nonspecific non-allergenic stimuli: cold air, exertion, pungent smell, stress, etc. Daily variability of peak expiratory flow rate of 20 % or more is one of the important indicators of hyper reactivity which is used to assess the severity of asthma [4, 5].

The aims of asthma treatment, regardless of the age of the patient, should be the complete elimination or significant reduction of symptoms, achieving the best possible respiratory function parameters, reduction in the number and severity of exacerbations, treatment optimization of the disease itself and its complications and comorbidities, the rational use of medications.

Following kinds of medications are used for the treatment of asthma:

1. The disease-controlling agents. These include inhaled corticosteroids (ICS), leukotriene modifiers, inhaled  $\beta_2$ -agonists, long-acting theophylline, cromones, systemic glucocorticoids (GC), and preparations for antiIgE therapy or allergen immunotherapy. Some of these drugs are taken daily and long-term to prevent symptoms of the disease because of their anti-inflammatory action and provide the control of inflammation in the bronchial tree.

2. Emergency treatment medications or “drugs on demand”. They act quickly, arresting symptoms and used as required. This group includes: fast-acting  $\beta_2$ -agonists, inhaled anticholinergics, systemic corticosteroids (CS), theophylline, and oral  $\beta_2$ -agonists of short action. Even with

very good control of asthma there is no guarantee complete absence of symptoms and exacerbations. Contact with an allergen, including unexpected stay in smoke-filled room and other similar situations can cause dyspnea, coughing and sudden development of asthma attack. This can happen anywhere and at any time, so it is important to have a means of emergency care and, of course, be able to apply them [5, 8]. The best formulation of medicines for the treatment of obstructive lung disease is inhalation.

Short-acting (4–6 h)  $\beta_2$ -agonists are widely used: fenoterol, salbutamol. Recently prolonged (12 h)  $\beta_2$ -agonists have become widely used (formoterol, salmeterol) [6, 7].  $\beta_2$ -agonists are the drugs that have fast and pronounced bronchodilating effect, primarily on the level of the small bronchi. Patients in most cases report relieved breath immediately after the use  $\beta_2$ -agonists. Bronchodilating effect of  $\beta_2$ -agonists is provided by  $\beta_2$ -receptors stimulation of smooth muscle cells. Furthermore, due to increased cAMP concentration  $\beta_2$ -agonists influence not only bronchial smooth muscle relaxation, but also the acceleration and beating cilia function improving ciliary clearance. Bronchodilating effect is higher when bronchial obstruction is more distal. After applying  $\beta_2$ -agonists patients feel a significant improvement in a few minutes and this positive effect is often overestimated. [9]  $\beta_2$ -agonists have arrhythmogenic action, may exacerbate coronary insufficiency, and contribute to high blood pressure. Moreover, when used in a long-term they may lose efficiency because of the blockade of  $\beta_2$ -receptors. Inhaled anticholinergic agents (AHA) for the treatment of asthma are presented with ipratropium bromide formulations (duration of action 6–8 h), which provides bronchodilating effect by means of M-holinoretseptors blocking and reduce of vagal tone. AHA inhibit bronchoconstriction, thus their level of activity depends on the severity of bronchi muscles reaction. But the mechanism of anticholinergic agents' action in asthma is not limited to the effect on smooth muscle tone [8, 10]. The secretion of bronchial mucus plays an important role in their action. It is known that direct or indirect cholinergic stimulation in respiratory tract causes activation of the submucosal glands and goblet cells secretory function, which increases bronchial obstruction in asthma. Anticholinergic agents may improve patency in peripheral parts of the broncho-pulmonary system by limiting the secretion of bronchial mucus. Modern AHA are characterized by the ability of full and long-lasting binding of muscarinic acetylcholine receptors, and therefore these compounds almost have no central properties but increased peripheral cholinolytic activity. They are well tolerated, rarely cause side effects, have no cardiotoxicity and their long-term use distinctly improve pulmonary ventilation and inhibit bronchoconstriction [11]. Anticholinergic agents are inferior to  $\beta_2$ -agonists by strength and speed. The onset of their bronchodilator action develops in 30–40 minutes after inhalation. However, sharing them with  $\beta_2$ -agonists provides mutually reinforcing effects of these medicines, has a pronounced bronchodilating effect, especially in moderate to severe asthma, as well as in patients with concomitant chronic obstructive bronchitis. Such a combined preparation containing ipratropium bromide and short-acting  $\beta_2$ -agonist is Berodual.

Berodual – combined preparation with pronounced bronchodilating effect, due to the action of its constituent fenoterol and ipratropium bromide. The mechanism of action  $\beta_2$ - agonist fenoterol is associated with activation of the conjugated with adrenoceptor adenylate cyclase resulting in increased cyclic AMP formation, stimulating calcium pump and, as a consequence, reducing a calcium concentration in myofibrils and subsequent bronchodilation. Ipratropium bromide is an M-holinoretseptors blocker, which ability to eliminate bronchoconstriction is associated with the influence of the vagal tone, when inhaled causes bronchodilation due mainly to local but not general anticholinergic impact [12, 13]. No adverse effect on the secretion of mucus in the airways, mucociliary clearance and ventilation.

Added to the AHA  $\beta_2$ -agonist enhances its bronchodilation effect. Both active components of Berodual N (fenoterol and ipratropium bromide) relax bronchial smooth muscle by targeting different levels, as a result their bronchodilating effect is enhanced. The combination of complementary components provides a pronounced bronchodilating effect using only half of preparation Berotek N fenoterol dose (50 mg), which minimizes the chance of adverse effects (as a rule, they appear only if overdose). Therefore, you can prescribe Berodual to patients with concomitant diseases of cardiovascular system [13, 14].

The combination of pharmacological components ensures Berodual N has:

- more pronounced and prolonged bronchodilating effect than each of the components;
- wide range of indications, including asthma, chronic obstructive bronchitis and a combination of these diseases in one patient;
- better safety profile in the case of cardiovascular comorbidity than  $\beta_2$ -agonists monotherapy;
- convenience for patients and cost-of-treatment benefit compared with the use of two separate aerosols;
- the possibility of using it both as an aerosol and nebulizer;
- lack of tachyphylaxis during long-term use.

Many patients with asthma prefer to use it to relieve symptoms Berodual N. Equally important is the influence in BA with predominant influence of parasympathetic nervous system, so-called "cholinergic asthma". Its features are advanced age of patients (usually, but not always), excessive sweating, hyperhidrosis of the palms, the frequent combination with peptic ulcer disease, the prevalence of attacks in the night and morning hours, often – productive cough with frothy sputum mucosa, expressed nonspecific response to provocative factors (physical exercise, cold air, strong odors), the cardiovascular symptoms – tendency to bradycardia, hypotension and arrhythmia. If patient has signs of "cholinergic asthma", the use Berodual N effecting the parasympathetic tone and containing small doses of short-acting  $\beta_2$ -agonist should be considered. Berodual N is effective in the treatment of asthma accompanied with chronic obstructive pulmonary disease (COPD) [9, 16]. During exacerbation of asthma on a background of viral respiratory infections, parasympathetic regulation of bronchial tone violation occurs associated with dysfunction

of receptors; that justifies the use of Berodual N to cope with the symptoms of obstruction.

In asthma, inhaled Berodual N should not be recommended for permanent use as a basic therapy. During an exacerbation it is used as one of the drugs of first choice in combination with basic ICS therapy and in remission it can be used as needed to prevent bronchoconstriction caused by exercise or exposure to allergen.

The idea of creating a combined bronchodilator, two components of which would target different mechanisms of bronchoconstriction was good and provided a successful use of the medication for many years. Properties of Berodual were studied comprehensively in numerous studies, most of which were conducted in the early years of its application. It has been shown that the combination of fenoterol hydrobromide / ipratropium bromide in patients with asthma in the first day resulted in a pronounced bronchodilating effect that persisted for 3 months, and did not cause tachypnoea. Comparison of the results both single application, and long-term treatment with salbutamol and fenoterol hydrobromide / ipratropium bromide combination in patients with bronchoobstructive diseases revealed advantage of a combined preparation which showed better efficacy (reduction of cough, dyspnea during the day and at night, preventing episodes of bronchoconstriction, less need for additional bronchodilator) and higher patients' compliance [17–19].

Berodual N is available in a metered dose CFC-free inhaler and solution for nebulizer forms. Dose inhaler Berodual N contains a single dose of ipratropium bromide (20 mg) and fenoterol hydrobromide (50 mg). It has less marked adverse effects, because the dose of  $\beta_2$ -agonist is less – a half than in standard inhalers, and the combination of two formulations potentiate each other's effect. Fenoterol's onset of action is in 4 minutes, the maximum effect is observed after 45 minutes, duration of action is 5–6 hours.

The creators of Berodual regularly modify its formulations to meet up-to-date requirements.

In accordance with modern standards of environmental safety at the end of the XX century, a new pressurized metered dose inhaler (MDI) – Berodual N containing safe for the ozone layer propellant tetrafluoroethane appeared. Numerous comparative studies of the freon and CFC-free MDIs Berodual revealed no significant differences in their efficacy and safety for patients [21–23]. In addition, a new generation of MDIs does not have a cooling effect on the mucous membranes of the respiratory tract, which was peculiar freon-containing inhalers.

Berodual can also be used as a solution for nebulization. Absolute indication for nebulizer therapy is the inability of drug delivery to the respiratory tract by any other inhalation device. The recommended dose of Berodual extemporaneously diluted with saline to a volume of 3–4 ml and nebulized for a few minutes until the solution is completely consumed. Nebulized inhalations of Berodual are widely used in intensive care patients with acute exacerbations of asthma and COPD of any severity, as well as prescribed for routine treatment in cases where patients cannot fully use

them or contraindicated dose inhaler (small children, elderly patients, etc.) [17, 18]. Indications for use of nebulized Berodual arise in cases where there is a need for high doses of bronchodilators, coordination difficulties of MDI inhalation and breath, with  $FEV_1 < 1$  liter or subjective nebulizer preference. Berodual is suitable for use in both clinical and ambulatory practice. High safety of Berodual enables its widespread use and young children, and elderly patients [22].

Use of Berodual N showed the efficacy and safety, including in patients with concomitant diseases of the cardiovascular system. Side effects are negligible, and arise mainly when overdosed, even if doses are excessively high, cardiotoxic reactions are not observed. Berodual MDI can be used in children from 6-year age and Berodual solution – from the first days of life, which indicates a high safety profile of the medication. Despite new combinations of long-acting bronchodilators emergence, this original combination has not lost its value and retains a dominant position in the treatment of asthma.

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## МІСЦЕ ПРЕПАРАТУ БЕРОДУАЛ В ЛІКУВАННІ БРОНХІАЛЬНОЇ АСТМИ

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**Резюме.** У статті йдеться про використання препарату Беродуал в лікуванні хворих на бронхіальну астму. Доведено, що його використання є ефективним і безпечним, у тому числі у пацієнтів із супутніми захворюваннями серцево-судинної системи. Побічні ефекти є незначними і виникають, головним чином, у разі передозування, при цьому навіть у дуже високих дозах не відмічається кардіотоксичних реакцій. Дозований аерозольний інгалятор Беродуал H можна призначати дітям з 6 років, а Беродуал розчин – з перших днів життя, що свідчить про високий профіль безпеки препарату.

**Ключові слова:** бронхіальна астма, Беродуал.

## BERODUAL® IN TREATMENT OF BRONCHIAL ASTHMA

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**Summary.** In the article the question is the use of the drug Berodual in the treatment of patients with bronchial asthma. It is proved that its use is effective and safe, including patients with concomitant diseases of the cardiovascular system. Side effects are minor and mainly occur in case of overdose, even in very high doses is not observed cardiotoxic reactions. Metered-dose aerosol inhaler Berodual H can be assigned to children from 6 years and Berodual solution – from the first days of life, it indicates a high safety profile of the drug.

**Key words:** bronchial asthma, Berodual.

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