Varieties of Pharmacological Treatment of Bronchial Asthma

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ABSTRACT

One of the most common chronic diseases in both adults and children is bronchial asthma (BA). It not only reduces the quality of life of patients, but can also lead to disability [1]. Late diagnosis and inadequate therapy are the main causes of severe course and high mortality from this disease. Modern asthma therapy is aimed at eliminating allergic inflammation of the bronchial mucosa, reducing bronchial hyperreactivity, restoring bronchial patency and eliminating bronchospasm, and preventing structural changes in the bronchial wall [2].

Keywords: bronchial asthma, children, pharmacotherapy, broncho spasmolytics, chromones, glucocorticosteroids, fixed combination, control

Introduction. Asthma in children is based on chronic allergic inflammation of the bronchi, accompanied by their hyperreactivity and recurrent bouts of difficulty breathing or suffocation as a result of widespread bronchial obstruction caused by bronchoconstriction, mucus hypersecretion, and edema of the bronchial wall [1, 2].

The leading role in the pathogenesis of AD belongs to mediated reactions leading to the development of allergic inflammation [3]. Inflammation of the airways in asthma is accompanied by a structural reorganization of the bronchial wall, which is accompanied by a thickening of their walls due to hypertrophy of smooth muscles, changes in epithelial cells, submucosa, vessels, and adventitia. Inflammation is persistent and persists in the intervals between exacerbations.

Main part. Allergic inflammation of the respiratory tract, which develops in asthma, causes the development of bronchial hyperreactivity and their obstruction. The disease is characterized by the occurrence of recurrent bronchial obstruction associated with exposure to both allergens and nonspecific factors. The presence of BA is confirmed by the violations of the ventilation function of the lungs of the obstructive type, revealed during the examination of patients, their decrease in the appointment of bronchospasmolytic drugs, as well as the detection of signs of bronchial hyperreactivity [1].

With an exacerbation of asthma, bronchial obstruction occurs. Characteristic is the presence of expiratory dyspnea, accompanied by noisy wheezing, sometimes audible at a distance. At the height of the attack, there is a cough with sputum that is difficult to pass. During an asthma attack, the chest expands with a decrease in the amplitude of breathing. When inhaling, retraction of the intercostal spaces and supraclavicular fossae is noted. The muscles of the shoulder girdle, abdominal wall, and back participate in the act of breathing. Older children and adolescents may complain of a feeling of constriction behind the sternum. During an asthma attack, examination reveals a boxed tone of percussion sound and lowering of the lower borders of the

lungs; auscultation reveals an abundant amount of wheezing against the background of an extended exhalation [4].

The resulting violation of bronchial patency can be manifested by mild, moderate and severe exacerbation (attack) of BA. The intensity of the developed allergic inflammation of the bronchi in children may not coincide with the clinic and the severity of the course of BA [4].

Persistent inflammation of the respiratory tract in patients with asthma can lead to severe exacerbations of the disease, manifested either by frequent attacks or by a pattern of prolonged (more than 6-8 hours) violation of bronchial patency in the form of an asthmatic condition with the development of respiratory failure, impaired drainage function of the lungs. A manifestation of mild asthma can be its cough variant, characterized by the occurrence of spastic cough. In children with a severe course of the disease, there may be a decrease in the functional activity of the adrenal cortex. In recent years, a severe form of BA has been more frequently recorded in adolescents, which is often associated with non-compliance with the regimen of basic anti-inflammatory therapy [1].

In children, asthma should be differentiated from the following diseases: obstructive bronchitis, bronchiolitis , recurrent stenosis of the upper respiratory tract, gastroesophageal reflux, tuberculous bronchoadenitis, tumors, laryngotracheomalacia , bronchopulmonary dysplasia, cystic fibrosis , bronchiolitis obliterans , pulmonary edema, vascular malformations, chlamydial infection, foreign body in the bronchi.

Therapy for asthma should be aimed at eliminating the symptoms of the acute phase of the disease, reducing the frequency and severity of exacerbations, achieving a stable clinical and functional remission of the disease, maximizing the improvement of lung functions, ensuring the normal development of the child and the proper quality of life [4].

Of great importance in the treatment of children suffering from asthma is the control of the patient's environment. It is necessary to carry out a set of measures aimed at preventing contact with causally significant allergens, reducing the concentration of aeroallergens in residential premises, and preventing the impact of nonspecific factors that cause an exacerbation of the disease [1].

The main goal of BA pharmacotherapy in children is to achieve stable (sustainable) remission and high quality of life in all patients, regardless of severity.

Therapy for acute asthma in children is carried out taking into account the severity of bronchial obstruction disorders and its duration. Objective information about the severity of bronchial obstruction can be obtained by determining the maximum volumetric flow rate (MOS) of expiration, because. the decrease in this indicator is directly correlated with the severity of the developed BA exacerbation. The value of MOS exhalation from 50 to 80% of the proper values indicates the presence of moderate or mild violations of bronchial patency. Expiratory MOS values less than 50% of normal values indicate the development

The goal of basic (anti-inflammatory) therapy is to achieve clinical and functional remission of the disease by removing allergic inflammation of the respiratory tract and preventing its occurrence. In cases of severe exacerbations of the disease, an x-ray examination of the lungs should be performed, in which, in some cases, atelectasis is detected, accompanying the inflammatory process in the lungs.

The most effective drugs for relieving asthma exacerbation are inhaled β2 agonists (Salbutamol , Berotek). They have significant bronchospasmolytic activity, have a therapeutic effect 10-20 minutes after inhalation of the drug. These medications can be administered using portable metered dose inhalers, spacers , nebulizers . Three types of devices are used in children: breath-actuated metered-dose aerosol inhalers (breath-activated MDIs), nebulizers , and dry powder inhalers (PIs). In children from 7 years of age, who are able to fully master the technique of using an inhaler, inhalation of salbutamol or berotek using metered-dose inhalers is most

effective. In children under 7 years of age and in patients with severe asthma exacerbation, treatment with inhaled β2 agonists using spacers and nebulizers is effective . Therapy with nebulizers is carried out with solutions of bronchospasmolytics (Ventolin , Berotek , Berodual).

With mild attacks of asthma, oral administration of bronchospasmolytics (Ventolina , Eufillina, Ascoril) is possible. In severe asthma attacks, combined therapy with inhaled bronchospasmolytics and glucocorticoids . Methods of choice for glucocorticosteroid therapy are nebulizer therapy with Pulmicort (budesonide), parenteral administration of glucocorticosteroids , as well as a short course of treatment with oral prednisolone for 3-5 days. With combined nebulizer therapy with bronchospasmolytics and Pulmicort , the bronchospasmolytic agent is first inhaled in the form of an aerosol, and then Pulmicort . An alternative to the inhalation administration of Pulmicort can be parenteral (intramuscular or intravenous) administration of glucocorticosteroids - Prednisolone, Methylprednisolone or Dexamethasone .

In an asthmatic condition, nebulizer therapy is carried out with inhaled β2 agonists in combination with inhaled pulmicort or parenteral administration of glucocorticosteroids . With insufficient effectiveness of this therapy or the inability to carry out nebulizer therapy , infusion therapy with aminofillin and glucocorticosteroids (Prednisolone, Methylprednisolone , Hydrocortisone, Dexamethasone) is prescribed. It is advisable to carry out long-term infusion therapy with aminophylline under the control of determining the concentration of theophylline in the blood serum, which allows maintaining optimal therapeutic concentrations of theophylline in the blood and preventing the development of side effects. Infusion therapy with aminofillin and glucocorticosteroids is carried out until the patient is removed from the asthmatic state.

In cases of development of severe and prolonged exacerbations of BA, a short, within 5-7 days, course of oral therapy with prednisolone at a dose of 1-2 mg/kg/ day should be carried out . If severe respiratory failure occurs, accompanied by involvement of the accessory muscles in the act of breathing, hyperinflation of the chest, the appearance of a paradoxical pulse, more frequent (every hour) inhalations of β2 agonists are carried out, and in the case of a rapid increase in respiratory failure, inhalations of β2 agonists are carried out three times after 15-20 minutes . Instead of inhalation, β2 agonists can be administered subcutaneously three times after 15-20 minutes in a 0.1% solution of adrenaline (0.1-0.3 ml). At the same time, the patient is prescribed oxygen therapy . If this therapy is ineffective and there is a threat of asphyxia, sick children are transferred to artificial lung ventilation.

Bronchial obstruction that occurs during exacerbation of BA is largely due to the accumulation of poorly discharged thick viscous sputum in the lumen of the bronchi. In this regard , therapeutic measures aimed at improving the discharge of sputum from the respiratory tract are of great importance . This is facilitated by the appointment of a vibration massage, inhalation of 2-4 ml of saline, mucolytic drugs (ambroxol) through a nebulizer up to 4 times a day. If it is impossible to independently discharge sputum from the bronchi, therapeutic bronchoscopy is used as a last resort, with bronchial washing with saline and its subsequent suction. The liquefaction of sputum and its discharge is facilitated by a sufficient intake of fluid in the body.

Oral administration of mucolytic and expectorant drugs: Fluifort , Broncholitis . In clinical practice, the most indicative in the treatment with inhaled glucocorticosteroids is the reduction in the frequency of exacerbations and hospitalizations, it is assumed that inhaled corticosteroids have an effect on reducing mortality from asthma.

The basis of asthma treatment is basic (anti-inflammatory) therapy - regular long-term use of drugs that stop allergic inflammation in the mucous membrane of the respiratory tract and prevent its occurrence.

The means of basic therapy include: inhaled glucocorticosteroids (IGCS), both as

monotherapy and in combination with prolonged β2 agonists, systemic corticosteroids, cromoglycic acid, sodium nedocromil , antileukotriene drugs. Durant theophyllines and some antiallergic drugs are used as additional means for controlling the symptoms of asthma . A special place is occupied by specific immunotherapy (ASIT). The volume of basic therapy depends on the severity of BA, the age of sick children, and the nature of comorbidities. The inflammatory process in the bronchi is detected not only during an exacerbation, but also in the remission phase, and therefore it is necessary to use anti-inflammatory drugs for a long time to prevent asthma exacerbations.

Currently, corticosteroids have been proven to be the most effective drugs for controlling asthma . inhalation glucocorticosteroids at recommended doses are well tolerated and considered safe drugs. According to the recommendations of international consensus documents (ShL 2002, 2006), inhaled corticosteroids are indicated for all patients with persistent BA. The reasons for the early appointment of inhaled glucocorticosteroids in asthma are the following: 1) inflammation of the respiratory mucosa is present even in the earliest stages of asthma; 2) ICS are the most effective anti-inflammatory drugs in AD compared with other known drugs; 3) the abolition of inhaled glucocorticosteroids in patients with asthma can lead to an exacerbation of the disease; 4) ICS prevent the progressive decline in lung function that occurs in patients with asthma over time [2].

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Modern AD therapy is based on a “stepwise” approach to drug treatment, the essence of which is to increase or decrease the amount of therapy depending on the severity and control of the symptoms of the disease. With insufficient control, the volume of therapy increases by a step. 3 months after achieving clinical and functional remission, the volume of therapy can be reduced by a step. When choosing treatment tactics and drawing up a plan for managing patients in short-term and long-term programs, the fundamental criterion is the severity of asthma. To assess the severity of BA, the following indicators are used [2]: characteristics of daytime and nighttime symptoms; tolerance for physical activity; frequency of use of short-acting β2 agonists; value of peak expiratory flow (PSV) or forced expiratory volume in 1 second (FEV 1); daily fluctuations (variability) of PSV.

Light intermittent asthma is characterized by rare exacerbations, which mainly occur when exposed to allergens, non-specific factors, sometimes after physical exertion. When conducting a study of the function of external respiration, they do not show violations of bronchial patency. In this regard, children with mild intermittent BA usually do not receive basic therapy with anti-inflammatory drugs (stage 1). But if such patients have other clinical manifestations of atopy (atopic dermatitis, allergic rhinitis, etc.), it is advisable for them to carry out therapy with broad-spectrum antiallergic drugs (Ketotifen or Cetirizine) that have anti-inflammatory activity. If necessary, inhaled fast-acting agonists (salbutamol , fenoterol) are used in 1-2 doses.

Light persistent BA is characterized by attacks of shortness of breath less than 1 time per week, stopped by taking a bronchodilator ; nocturnal attacks are absent or rare. In patients with mild persistent asthma (stage 2), cromones are used for anti-inflammatory therapy for at least 3 months: Intal , administered as a powder using a spinhaler , or an aerosol delivered to the respiratory tract by a metered dose inhaler; Kromoheksal solution through a nebulizer ; Tailed . Fast -acting β2 agonists are used on demand. It should be noted that treatment with cromones is quite effective in a significant number of patients with mild atopic BA. Improvement in asthma control in children can be achieved by prescribing long-acting β2 agonists or sustained-release theophylline along with

cromones . With an insufficient effect of cromones and a continuing need for short-acting β2 agonists, low or medium doses of ICS are used using large volume spacers (0.75 l). Accordingly, the severity of the disease is reviewed and treatment is carried out in accordance with the 3rd stage.

Moderate asthma is characterized by attacks of shortness of breath, recurring more than once a week, but not daily, which are stopped by the repeated use of bronchodilators , and sometimes glucocorticosteroids . Nocturnal seizures are characteristic, exercise tolerance is limited. In children with moderate and severe asthma, inhalation of glucocorticosteroids (budesonide , beclomethasone) is performed as basic therapy. dipropionate , fluticasone propionate), which have the highest anti-inflammatory activity. If necessary, they can be used for a longer time. Such therapy contributes to the achievement and maintenance of clinical remission of the disease.

Of all inhaled corticosteroids, budesonide has the most favorable therapeutic index , due to its high affinity for glucocorticoid receptors and accelerated metabolism after systemic absorption in the lungs and intestines. Today, budesonide is the only inhaled corticosteroid with proven once-daily use. A long-term randomized study lasting about 9 years did not reveal the effect of continuous treatment with budesonide at a dose of 400 μg/ day on the linear growth of children [1]. Registered in Russia inhaled GCS Tafen Novolizer (budesonide) has a pronounced local anti-inflammatory effect on the bronchial mucosa and has a weak systemic effect. The drug inhibits the activity of cells involved in inflammatory reactions (mast cells, eosinophils, neutrophils, macrophages, lymphocytes), and also releases inflammatory mediators (histamine, eicosanoids , leukotrienes , cytokines), which leads to the restoration of respiratory function and a decrease in bronchial hyperreactivity. Tafen novolizer (budesonide) is available as a metered powder for inhalation of 200 mcg/1 dose (200 dose cartridge with or without inhaler). The drug is prescribed from 6 years. Children 6-12 years of age are prescribed 200 mcg 1-2 times a day (1-2 doses per day). The maximum daily dose is 800 mcg (4 doses). Adults and children over 12 years of age are prescribed 200 mcg 1-2 times a day (1-2 doses per day). The maximum daily dose is 1600 mcg (8 doses). If the daily dose exceeds 800 mcg (4 doses), it is divided into 3-4 doses.

When starting therapy in patients with moderate BA (stage 3), it is preferable to prescribe low and medium doses of ICS , as well as their combinations with prolonged β2 agonists (formoterol and salmeterol , the duration of which is more than 12 hours). The use of the latter is more preferable than increasing the dose of iGCS over 400 mcg. It is possible to combine inhaled corticosteroids with drugs for oral administration (anti-leukotriene drugs (Acolat , Singulair), durant theophyllines) [2, 4, 5]. In some patients, it is possible to achieve remission with the use of cromones . In these cases, it is advisable to revise the severity of BA (reduce by a step). If it is not possible to achieve asthma control using therapy within the 3rd stage, or the patient has frequent symptoms, a constant need for bronchodilators and / or a decrease in PEF, PEF variability is high, then prescribe treatment in the 4th stage and review the severity of the disease.

Severe asthma is characterized by frequent, several times a week, or daily, several times a day, attacks, incl . nocturnal symptoms. Attacks are usually severe, stopped by a combination of bronchodilators and glucocorticosteroids , exercise tolerance is significantly reduced, and sleep is disturbed. For the basic therapy of severe BA (stage 4), the use of inhaled corticosteroids in medium and high doses is required. As initial therapy, combined preparations with fixed combinations of glucocorticosteroids and prolonged β2 agonists (budesonide + formoterol ; flixotide + salmeterol) are prescribed. Adding β2 agonists is preferable to increasing the dose of glucocorticosteroids . Alternative regimens for stage 4 include combinations of high-dose glucocorticosteroids with antileukotriene drugs and durant theophyllines. Upon reaching clinical

remission, the dose of inhalation glucocorticosteroids may be reduced.

For children with uncontrolled asthma, it is preferable to start treatment with combined preparations containing glucocorticosteroids and durant β2 agonists, which allows to achieve a faster therapeutic effect and treat with low doses of corticosteroids . An increase in the intake of the latter in the lungs, as well as a decrease in the incidence of candidal infection in the pharynx and larynx, which sometimes occurs as a complication in the treatment of inhaled glucocorticosteroids , and the use of spacers contributes to reducing the risk of developing a systemic effect of glucocorticosteroids .

A fixed combination of iGCS and prolonged β2 agonists in one inhaler has a synergistic effect associated with the peculiarities of their mechanism of action at the cellular and molecular level. Glucocorticosteroids reduce the desensitization and tolerance of β2 receptors and increase the synthesis of β2 receptors in the bronchi; prolonged β2 agonists stimulate the inactive glucocorticosteroid receptor through the phosphorylation mechanism, as a result of which it becomes more sensitive to steroids. Therapy with drugs with a fixed combination of inhaled corticosteroids and prolonged β2 agonists is more effective and has a more pronounced anti-inflammatory and bronchodilatory effect compared to the simultaneous use of two drugs in separate inhalers. In this regard, it is mainly used as a basic therapy. At present , significant progress has been made associated with the use of combined preparations containing anti-inflammatory and bronchodilator components. Combination preparations Seretide (salmeterol + fluticasone) are registered and used in Russia . propionate), Symbicort (formoterol + budesonide) and the newly registered drug Foster (formoterol + beclomethasone).

Combination preparation Seretide contains salmeterol and fluticasone propionate , which have different mechanisms of action: salmeterol prevents the occurrence of bronchospasm , fluticasone propionate improves lung function and prevents exacerbations. Seretide is used in children from 4 years of age. The drug is available in the form of a powder inhaler " Multidisc ", each dose of which contains 50 micrograms of salmeterol xinafoate in combination with 100, 250 or 500 mcg of fluticasone propionate , as well as a freon-free metered-dose aerosol inhaler (MAI) containing 25 micrograms of salmeterol per dose xinafoate in combination with 50, 125 or 250 mcg of fluticasone propionate . If it is necessary to increase the dose, an inhaler with a higher dose of fluticasone is used. propionate and the same dose of salmeterol . The efficacy and safety of Seretide have been demonstrated in randomized controlled trials in more than 4200 children and adults with varying degrees of asthma. It has been shown that Seretide is more effective than monotherapy with each of its components, and at least as effective as both drugs used simultaneously, but in different inhalers [6].

Systemic glucocorticosteroids for long-term treatment are currently rarely prescribed. In extremely severe cases (stage 5), glucocorticosteroids (preferably Prednisolone) are prescribed orally at a daily dose of 1 mg / kg. Transfer of patients with long-term systemic therapy glucocorticosteroids at high doses of glucocorticosteroids are carried out under the control of adrenal function with the gradual withdrawal of Prednisolone starting from the evening dose. After stabilization of the patient's condition, glucocorticosteroids are prescribed taking into account the daily rhythm. In critically ill children, the dose of prednisolone should be reduced very carefully and gradually to prevent withdrawal syndrome. A forced reduction in the dose of corticosteroids or their complete cancellation without taking into account the child's condition can lead to the development of asphyxia .

Conclusion . Given the undulating course of the disease, it is necessary to constantly monitor its course and carry out timely correction of the therapy. In the latest edition of GINA (2006), along with the severity of the disease, it is proposed to single out the level of control over the disease. However, experts in

the field of childhood asthma offer other approaches that take into account both the characteristics of the course of this disease in children and the age of the child. In accordance with the practice guidelines of the consensus document on the diagnosis and management of asthma in children PMC-LL (2008), good control of the course of the disease is observed when the following results are achieved: daytime symptoms appear 2 or less than 1 time per week; daily and physical activity are not limited; nocturnal symptoms occur 0-1 time per month or 0-2 times per month if the child is older than 12 years; rescue drugs are used 2 or less times a week; lung function is normal (if it can be assessed); there has been no more than 1 exacerbation in the past year. Good control of asthma in children of any age implies a persistent (at least 3 months) absence of symptoms of the disease. According to these recommendations, in children older than 2 years, the algorithm for treating asthma includes the use of cromones , antileukotriene receptor antagonists, and inhaled glucocorticosteroids as first-line drugs for basic therapy . Treatment of children with asthma under 2 years of age begins with the use of cromones and inhaled corticosteroids , the doses of which are selected individually. After achieving control over the disease, the doses of inhaled corticosteroids are reduced to the minimum . To control asthma , iGCS or cromones are used .

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