USE OF ANTILEUKOTRIENE DRUGS IN PEDIATRICS

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Abstract. *The effects of glucocorticosteroids in the respiratory tract and their systemic effects depend more on the inhalation device used. Given that inflammatory and remodeling processes occur in all parts of the respiratory tract, including distal parts and peripheral bronchioles, regardless of the state of bronchial permeability and compliance with requirements, the optimal method of drug delivery to the lungs the question arises. The preferred particle size of the inhaled drug, which ensures uniform distribution in large and distal bronchi, is 1.0-5.0 μm for adults and 1.1-3.0 μm for children.*

Keywords: *pharmacodynamics of antileukotriene drugs in children, mechanism of action, instructions for use.*

Drug delivery methods are constantly being improved in order to reduce the number of errors related to breathing techniques, which in turn reduce the effectiveness of treatment and increase the frequency and severity of side effects. A metered dose inhaler (MAI) can be used intermittently. Nebulizer use can effectively stop exacerbations of bronchial asthma (BA) in the outpatient setting, reducing or eliminating the need for infusion therapy.

In accordance with the international treaty for the preservation of the earth's ozone layer (Montreal, 1987), all manufacturers of inhalation drugs switched to CFC-free metered-dose aerosol inhalers (MAIs). The new inducer norflurane (hydrofluoroalkane, HFA 134a) had a significant effect on the particle size of some inhaled glucocorticosteroids (IGCS), especially ciclesonide: a significant part of the drug particles was from 1.1 to 2.1 microns (external particles). has the size In this regard, IGCS in the form of PDI with HFA 134a has the highest percentage of lung deposition, for example, 52% for ciclesonide, and deposition in the peripheral parts of the lung is 55%.

The safety of inhaled glucocorticosteroids and the possibility of developing systemic effects depend on their systemic bioavailability (absorption from the gastrointestinal mucosa and absorption in the lungs), the level of the free fraction of the drug in the blood plasma (binding to plasma proteins) and is determined by the level of inactivation of GCS during primary passage through the liver (presence / absence of active metabolites).

Inhaled glucocorticosteroids are rapidly absorbed from the gastrointestinal tract and respiratory tract. Pulmonary absorption of glucocorticosteroids (GCS) can be affected by the size of inhaled particles, as particles smaller than 0.3 microns accumulate in the alveoli and are absorbed into the pulmonary circulation.

When using a metered-dose aerosol inhaler (MAI), only 10-20% of the inhaler dose is delivered to the respiratory tract, and up to 90% of the dose is collected and swallowed in the oropharyngeal region. In addition, this part of inhaled glucocorticosteroids (IGCS) is absorbed from the gastrointestinal tract and enters the hepatic circulation, where a large part of the drug (80% or more) is inactivated. Inhaled corticosteroids enter the systemic circulation mainly in the form of inactive metabolites. Therefore, systemic oral bioavailability for most inhaled

glucocorticosteroids (ciclesonide, mometasone furoate, fluticasone propionate) is very low, almost zero.

It should be remembered that part of the dose of ICS (about 20% of the nominal dose, in the case of beclomethasone dipropionate (beclometasone 17-monopropionate) - up to 36%), enters the respiratory tract and is quickly absorbed. In addition, this portion of the dose may cause extra pulmonary systemic side effects, especially when high doses of ICS are prescribed. In this regard, the type of inhaler used with ICS is not important, because when the dry powder of budesonide is inhaled through a Turbuhaler, the deposition of the drug in the lungs increases by 2 times or more compared to inhalation from the PDI.

For inhaled glucocorticosteroids (IGCS) with a high fraction of bioavailability through inhalation (budesonide, fluticasone propionate, beclomethasone 17-monopropionate), systemic bioavailability may increase in the presence of inflammatory processes in the bronchial mucosa. This was found in a comparative study of systemic effects on the level of reduction in plasma cortisol after a single administration of budesonide and beclomethasone propionate at a dose of 2 mg every 22 hours by healthy smokers and non-smokers. It should be noted that after inhalation of budesonide, cortisol levels were 28% lower in smokers than in nonsmokers.

Inhaled glucocorticosteroids (IGCS) have a very high binding to plasma proteins; in ciclesonide and mometasone furoate, this ratio is slightly higher (98-99%) than in fluticasone propionate, budesonide, and beclomethasone dipropionate (90, 88, and 87%, respectively). Inhaled glucocorticosteroids (IGCS) have a rapid clearance, the value of which is approximately the same as the value of hepatic blood flow, and this is one of the reasons for the minimal manifestation of systemic side effects. On the other hand, rapid clearance provides ICS with a high therapeutic index. The fastest clearance above the hepatic blood flow rate was found in desciclesonide, which leads to a high safety profile of the drug.

Thus, the main features of inhaled glucocorticosteroids (IGCS) can be distinguished, their effectiveness and safety depend mainly, especially during long-term therapy:
a large number of fine particles that ensure a high deposition of the drug in the distal parts of the lungs;

- high local activity;
- high lipophilicity or the ability to form fatty conjugates;
- low level of absorption into the systemic circulation, high binding to plasma proteins and high hepatic clearance to prevent the interaction of GCS with GCR;
- low activity of mineralocorticoids;
- high compliance and ease of dosing.
- Ciclesonide (Alvesco)

Ciclesonide (Alvesco) is a non-halogenated inhaled glucocorticosteroid (IGCS), a prodrug that is converted to the pharmacologically active form - desciclesonide - by esterase in lung tissue. Desciclesonide has 100 times greater affinity for the glucocorticoid receptor (GCR) than ciclesonide.

The reverse conjugation of descyclonide with highly lipophilic fatty acids ensures the formation of a depot of the drug in the lung tissue and maintaining an effective concentration for 24 hours, which allows Alvesco to be used once a day. The active metabolite molecule is characterized by high affinity, fast binding and slow release to the glucocorticoid receptor (GCR).

The presence of norflurane (HFA 134a) as a stimulant provides a significant fraction of ultrafine particles of the drug (size from 1.1 to 2.1 microns) and high deposition of the active substance in the small airways. Given that inflammatory and remodeling processes occur in all parts of the respiratory tract, including the distal parts and peripheral bronchioles, the question arises about the optimal method of drug delivery to the lungs, regardless of the state of bronchial permeability. .

In a study conducted by TV. de Vries and others, using laser diffraction analysis and the method of different inspiratory flows, a comparison of the delivered dose and particle size of different inhaled glucocorticosteroids was made: fluticasone propionate 125 μg, budesonide 200 μg, beclomethasone 10 μg (HFA) and 10.0 μg.

The mean aerodynamic particle size of budesonide is 3.5 μm, fluticasone propionate is 2.8 μm, and beclomethasone and ciclesonide are 1.9 μm. Ambient humidity and respiratory flow rate did not significantly affect particle size. Ciclesonide and beclomethasone (HFA) had the largest fraction of fine particles between 1.1 and 3.1 μm.

Because ciclesonide is an inactive metabolite, its oral bioavailability tends to be zero, preventing local adverse effects such as oropharyngeal candidiasis and dysphonia, which have been reported in several studies.

Ciclesonide and its active metabolite dessixonide are almost completely bound (98-99%) to plasma proteins when introduced into the systemic circulation. In the liver, desciclesonide is inactivated by the CYP3A4 enzyme of the cytochrome P450 system to inactive metabolites that are hydroxylated. Ciclesonide and desciclesonide have the fastest clearance among inhaled glucocorticosteroids (IGCS) (152 and 228 l/h, respectively), the value of which significantly exceeds the rate of hepatic blood flow and provides a high safety profile.

Inhaled glucocorticosteroids and combined means containing glucocorticosteroids

Currently, inhaled corticosteroids are the most effective drugs for controlling asthma, so they are recommended for the treatment of persistent asthma of any severity. exacerbation and improvement in the number of hospitalizations and quality of life improves respiratory function, reduces bronchial hyperreactivity and reduces bronchoconstriction during exercise. daytime and nighttime cough, wheezing and shortness of breath, physical activity, use of rescue medication and use of health system resources.

In children, the following ICS are used: beclomethasone, fluticasone, budesonide. The doses of drugs used for the main therapy are divided into low, medium and high. It is safe to take ICS in low doses, the possibility of side effects should be known when prescribing high doses. The equipotent doses presented in Table 2 were developed empirically, so the individual characteristics of the patient (response to therapy) should be taken into account when choosing and changing ICS.

Leukotriene receptor antagonists

Antileukotriene drugs (zafirlukast, montelukast) partially protect against exercise-induced bronchoconstriction for several hours after administration. Addition of anti-leukotriene drugs to treatment in cases of insufficient response to low doses of glucocorticosteroids provides clinical improvement, including a statistically significant reduction in the frequency of exacerbations. Antileukotriene therapy has been shown to be clinically effective in children older than 5 years with all grades of asthma, but these agents are generally less effective than low-dose ICS. Anti-leukotriene drugs can be used to augment therapy in children with moderate asthma when the

disease is not adequately controlled with low-dose glucocorticosteroids. Moderate improvement in lung function (in children 6 years and older) and control of BA (in children 2 years and older) with leukotriene receptor antagonists as monotherapy in patients with severe and moderate BA Note B will be done. Zafirlukast has a moderate effect on respiratory function in children aged 12 years and older with moderate to severe asthma A.

Anti-IgE drugs

This is a completely new class of drugs used today to improve the control of severe persistent atopic asthma. Omalizumab is the most widely studied, the first and only drug recommended for use in children over 12 years of age. The high cost of Omalizumab treatment, as well as the need for monthly visits to the doctor for drug injections, is justified in patients who require repeated hospitalization, emergency medical care, and the use of high doses of inhaled and / or systemic corticosteroids.

Long-acting methylxanthines

Theophylline is more effective than placebo in controlling asthma and improving lung function, even at doses below the recommended therapeutic range. However, the use of theophylline for the treatment of asthma in children is problematic because it can cause serious, immediate (cardiac arrhythmias, death) and delayed (behavioral disorders, learning problems) side effects. In this regard, the use of theophylline is possible only under strict pharmacodynamic control.

Long-acting β2-agonists, long-acting inhaled β2-agonists

This group of drugs is effective in maintaining BA control (Figure 1). They are routinely used only in combination with ICS and are prescribed only when standard initial doses of ICS fail to achieve asthma control. The effect of these drugs lasts for 12 hours. In the form of inhalation, formoterol shows its therapeutic effect (relaxation of bronchial smooth muscles) after 3 minutes, the maximum effect develops 30-60 minutes after inhalation. Salmeterol begins to act relatively slowly, a significant effect is noted 10-20 minutes after inhalation of a single dose (50 μg), and the effect after taking salbutamol appears after 30 minutes. Because of the slow onset of action, salmeterol should not be used to treat acute asthma symptoms. Since the effect of formoterol develops faster than the effect of salmeterol, this allows formoterol to be used not only for prevention, but also for the relief of asthma symptoms. However, according to GINA 2006 recommendations, long-acting β2-adrenergic agonists can only be used in patients receiving regular maintenance therapy with ICS.

Children tolerate treatment with long-acting inhaled β2-agonists, even with long-term use, and their side effects are comparable to short-acting β2-agonists (if needed). Medicines of this group should be prescribed only in combination with the main therapy of ICS, because monotherapy with long-acting β 2 -agonists without ICS increases the probability of death in patients! Due to conflicting data on the effects of asthma exacerbations, these drugs are not the drugs of choice for patients who should be prescribed two or more maintenance therapies.

Oral β2-adrenergic agonists are long-acting

Drugs in this group include long-acting salbutamol dosage forms. These medications help control asthma symptoms at night. They can be used as an adjunct to inhaled corticosteroids if standard doses of the latter do not provide adequate control of nocturnal symptoms. Possible side effects include cardiovascular stimulation, anxiety, and tremors. Medicines of this group are rarely used in pediatrics in our country.

Anticholinergic drugs

Inhaled anticholinergics are not recommended for long-term use (primary therapy) in children with respiratory problems.

Systematic GCS

Despite the fact that systemic corticosteroids are effective against AD, the development of adverse events such as depression of the hypothalamus-pituitary-adrenal system, weight gain, steroid diabetes, cataracts, and hypertension should be considered during long-term therapy along with growth retardation, immunosuppression, osteoporosis, mental disorders. Taking into account the risk of side effects with long-term use, oral corticosteroids should be used in children with asthma only in case of severe exacerbations, both against the background of a viral infection and in the absence of it.

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