Innovative phosphodiesterase inhibitor in the treatment of bronchial obstructive disease exacerbations

On March, 15-16 the traditional spring therapeutic readings took place in Vinnytsia. This year the program of the conference had a clear structure of the sections by a certain topic. Within the frames of the event clinicians paid much attention to the diagnosis and treatment of severe respiratory tract pathology.

It is obvious that the category of patients with exacerbation of bronchial asthma (BA) and chronic obstructive pulmonary disease (COPD) is one of the most difficult categories of patients with pulmonary disorders. Annually the updated recommendations for management of patients with BA and COPD - GINA and GOLD respectively - outline the main issues of basic treatment of patients with different forms and stages of these diseases. But, in spite of some success achieved during the recent years, emergence of new medicines and basic treatment systematization, it is impossible for now to avoid exacerbation periods in BA and COPD: therapeutic and pulmonary departments are always overfilled by patients with broncho-obstructive diseases in acute stage. This fact explains high attention of medical society to the possibilities of BA and COPD treatment optimization at hospital stage. This is the very topic that **the holder of Habilitation degree in Medicine, Professor of Tuberculosis and Pulmonology Department of National Medical Academy of Post-Graduate Education named after P. L. Shupik (Kyiv) Serhii Viktorovych Zaykov** paid attention to in his research**.**

- In modern literature a broncho-obstructive syndrome (BOS) is defined as a universal pathological condition for many lung diseases. It results in breathing air flow restriction and patients feel breath shortness (typically expiratory). Facultative BOS can occur in such respiratory disorders as acute bronchitis, pneumonia, tuberculosis, sarcoidosis, idiopathic fibrosis or pulmonary cancer pathology, as well as pneumoconiosis, pulmonary fungal infections, lesions of the lung tissue by helminthes/parasites. For some diseases of the respiratory tract, such as BA, COPD and emphysema of the lungs, BOS is an obligatory and the main syndrome.

Basic pathogenetic mechanisms of BOS include inflammation and swelling of the bronchial mucosa, unstriped muscle spasm, viscous mucus hypersecretion, peribronchial fibrosis, cicatricial stenosis of the bronchus, bronchial compression by emphysematous tissue. **It is important to mention that only first three mechanisms of listed above are inversum, so broncho-obstructive disease therapy should be aimed at thereof.**

Inflammation of the airways in the process of BOS formation is developed with contributions from epithelial and endothelial cells, granulocytes, macrophages, monocytes. T-cell activation in response to antigens may be observed. As a result of inflammation geometry violations of bronchial tubes occur in the airways through wall thickening, lumen closing with mucus, cellular detritus, increased release of proinflammatory cytokines; development of bronchial hyperreactivity; violations of neuroregulatory mechanisms. All this comprises an aggravating circumstance in acute and chronic respiratory diseases, and risk factors of prolonged duration and occurrence of exacerbations in the future.

How should one evaluate BOS in practice? Clinical criteria of BOS include choking, dry cough, cyanosis, supporting muscles involved in breathing, tympanitis, lengthening of exhalation, noisy breathing, dry sibilant rale. To confirm the presence of BOS and to assess its severity the functional methods are used, preeminently spirometry. Decrease in forced expiratory volume (FEV_1) <80% of the appropriate value is an indicator of respiratory function (RF), indicating the presence of BOS. The ratio of FEV_1 and forced vital capacity (FVC) after bronchodilatatory test - FEV/FVC <70% is the earliest sign of BOS, particularly in COPD. There are also a few tables that are used to determine the degree of BOS severity by means of a variety of indicators of spirometry and laboratory indicators data of blood gas composition.

While the diagnosis of BA and COPD is currently more or less clear (though, unfortunately, in Ukraine there is still a problem of late acquisition of bronchial obstruction), the treatment usually raises flags, despite quite clear recommendations today. Step by step treatment of BA is carried out in accordance with the current Order # 868 of the MoH of Ukraine dated 8 October 2013, and amended GINA recommendations (last edition in February 2017). Basic therapy of COPD is described in updated 2017 GOLD guidelines.

According to the approvals, the following medicinal products are considered as those that eliminate bronchial obstruction:

• medicinal products that reproduce the effect of adrenergic stimulation (sympathomimetics or B2-agonists of short (SABA - salbutamol, fenoterol) or long action (LABA - salmeterol, formoterol, indacaterol, vilanterol); there are also combinations of SABA and LABA);

• medicinal products that block bronchoconstrictive action of acetylcholine (cholinolytics or cholinergic antagonists) of short (ipratropium bromide) or long action (tiotropium bromide, glycopyrronium). Xanthine, inhibitors of phosphodiesterase (PDE) - theophylline comprise a special group.

Despite the variety of medicines, the treatment of patients with BOS remains a very difficult task, because bronchial spasmolytics (even in combination with inhaled glucocorticoids - IGC) are quite poorly effective or ineffective at hospital stage. What is the reason of this phenomenon? Today it is well-known that the frequent administration of P_2-adrenergic agonists at prehospital stage is the main reason for receptor desensitization and the resulting lack of effectiveness of SABA - first-line therapy. In addition, bronchial spasmolytics used to eliminate the aggravation of BA or COPD usually are able to control bronchospasm, but not the process of inflammation. And, as it is well known, that inflammation is the main inversum mechanism of BOS occurrence. So, the hospital stage for the rapid elimination of BOS should use an integrated approach (taking into account the therapy conducted in the prehospital stage) which will be able to provide elimination of both bronchospasm and inflammation.

A new drug for infusion therapy of exacerbations of bronchial obstruction diseases - Derkast® (Yuria-Pharm LLC, Ukraine) has recently become available on the pharmaceutical market of Ukraine. Derkast® is used to eliminate the exacerbations of COPD and BA at hospital stage. Complex effect of the product is directed against the two main mechanisms of BOS emergence - bronchospasm and inflammation. Derkast® inhibits PDE 3, PDE 4, PDE 5, and thereby broncholytic and anti-inflammatory effects are realized. Inhibition of PDE 3 and 5 in the cells of the bronchial unstriped muscles provides relaxation of thereof and inhibiting of PDE 4 in neutrophils, lymphocytes leads to inhibition of the synthesis of basic proinflammatory mediators. The advantage of medicinal product Derkast® is an advanced composition that fully ensures the disclosure of its potential as PDE inhibitor. Thus, magnesium and potassium ions that are part of Derkast, act as "catalysts" of main active ingredient.

How important is the sufficient quantity of these elements in successful elimination of aggravation of pathology accompanied by BOS? It turns out, that in BOS the decrease of the levels of magnesium and potassium in blood plasma is observed. In patients with BA and COPD the background shortage of these elements due to the use of basic treatment (bronchial spasmolytics, IGC, methylxanthines) and diuretics (Yang C.T., 1996) is observed. So, in a study of A.N. Nagdeot, Y.R. Pawade (2011) correlation between potassium and salbutamol administration in patients with BA was noted (Table 1). Hypoxemia in patients with acute exacerbation of BA and COPD is another cause of hypomagnesemia. In a study of M. Faris et al. (2015) electrolyte disorders with hypomagnesemia prevalence in patients with acute exacerbation of COPD are clearly demonstrated (Table 2).

Table 1. **Administration of salbutamol in patients with BA contributes to hypokalemia development**

Level of electrolytes	Before treatment with salbutamol (n = 50)	After treatment with salbutamol (n = 45)
Sodium (mmol/l)	138±3.4	139±3.8
Potassium (mmol/l)	4.13±0.46	3.6±0.42

Table 2. **Hypomagnesemia in patients with COPD exacerbation**

Electrolytes	Patients with COPD (n=60)	Control group (n=45)
Magnesium (mmol/l)	1.85±0.17	2.20±0.14
Potassium (mmol/l)	3.28±0.46	4.49±0.33
Calcium (mmol/l)	1.08±0.17	1.23±0.09

Electrolyte imbalance in patients with BA and COPD can lead to inefficient PDE inhibition, as well as it can be a risk factor for deterioration of patients' condition with acute exacerbation of asthma and COPD. This is because potassium and magnesium are essential trace elements necessary for the formation of cAMP, due to which the therapeutic effects of PDE inhibitors are realized (Fig.).

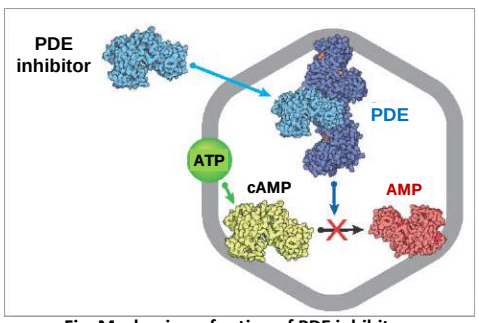

Fig. Mechanism of action of PDE inhibitors

Note: ATP is a macroergic compound formed by the catabolism of glucose (Krebs cycle, glycolysis, phosphorylation); cAMP is a derivative of ATP; intermediary that performs signaling inside the cell; AMP is a cAMP breakdown product.

Magnesium is involved in all stages of the Krebs cycle, resulting in the formation of ATP; it is part of 6 of 9 enzymes of glycolysis reactions; it activates adenylyl cyclase, which controls the synthesis of cAMP; it is required for the formation of cAMP.

Potassium further activates pyruvate kinase which catalyzes glycolysis with formation of ATP; it intensifies the action of enzyme systems involved in the synthesis of ATP in oxidative phosphorylation reactions.

Theophylline - 2 mg / ml, potassium chloride - 0.3 mg / ml, and magnesium chloride - 0.2 mg / ml are part of Derkast® composition.

Today Derkast® is the only parenteral drug for the treatment of moderate to severe exacerbations of BA and COPD at the hospital stage, allowing elimination of bronchospasm and inflammation.

It is interesting to present the results of domestic randomized study on the efficacy and safety of medicinal product Derkast®. 39 male and female patients aged 18-70 years with BA were enclosed. The observation period was 14 days, the total duration of the study reached 4 months. Patients received basic therapy. Derkast® was administered in a daily dose of 5 mL/kg (10 mg/kg of theophylline), in average - 600-800 mg of theophylline, divided into 3 administrations.

Entry criteria:

- age of 18-70 years;
- presence of moderate BA;
- daily exacerbations of BA;
- severity of exacerbation (and associated impairment of labor activity, physical activity and sleep disorders);
- the frequency of night symptoms > 1 time in a week;
- daily administration of SABA;
- peak expiratory flow rate (EFR (type)) 60-80% of the norm, daily fluctuations of EFR (type) > 30%;
- stable (controlled) BA progress during 3 months prior to inclusion in the study;
- constant use of GCI;
- informed consent for participation in the study;
- patient's ability to adequately cooperate during the study.

All patients were subject to clinical and anamnestic physical examination; clinical and biochemical blood tests, urinalysis, spirometry were prescribed (FEV_1, FVC, FEV_1/FVC, EFR, maximum expiratory flow at different moments of time - MEF_{25}, MEF_{50}, MEF_{75}).

Criteria of therapy effectiveness:

- main: dynamics of RF;
- additional: dynamics of clinical manifestations of BA, reduction of daily variability of EFR (type) in the process of treatment.

According to the study, Derkast® has demonstrated effectiveness in 36 patients (92.3%). Good or satisfactory tolerability of the drug took place in all patients with BA. No treatment termination took place.

It is worth emphasizing one more time that administration of Derkast® allows controlling exacerbation of bronchial obstruction disease even in "difficult" patients with poor response to the first line treatment.

Thus, therapy efficacy in patients with BA and COPD is mainly determined by the ability to control the severity of bronchial obstruction and inflammation. And the combined influence on these main BOS mechanisms is the key to success. Medicinal products of complex action that reduce / eliminate inflammation and bronchospasm have good prospects in helping patients with acute exacerbation of BA or COPD (especially at the hospital stage). Derkast®, medicine for infusions, an inhibitor of PDE with plasma concentrations of potassium and magnesium is one of such medicinal products.

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