Derkast®: a complex approach in the treatment of patients with BA and COPD during hospital care

Bronchial asthma (BA) and chronic obstructive pulmonary disease (COPD) belong to the diseases of the respiratory system, the treatment of which, unfortunately, is not always possible without hospitalization.
As a rule, an urgent care to such patients is provided with a focus on eliminating bronchial spasm in hospitals, which is a life-threatening condition. At the same time it is well known that progressive inflammation is the cause for the deterioration of health condition of patient during disease recurrence. This calls for the need to search for drugs, which could ensure the reliable control of inflammation in BA and COPD exacerbation. What are the special aspects of treatment of such patients in hospitals?

Chronic inflammation in the pathogenesis of BA and COPD

Under the terms of consensus "Global initiative for asthma" (Global initiative for asthma, GINA, 2017) BA is seen as a heterogeneous disease characterized by chronic inflammation of the airways which is diagnosed by respiratory symptoms namely wheezing, shortness of breath, tightness of the chest or coughing, which are variable as to duration and intensity combined with labile expiratory airflow obstruction. Pathogenesis of COPD ("Global Initiative for COPD" report – Global Initiative for Chronic Obstructive Lung Disease, GOLD 2017) also contains the information about the fact that an inflammatory process, as well as the imbalance of protease and antiproteinase in lungs, and oxidative stress are playing leading roles in the development of the disease. Herewith, chronic inflammation as in case of BA as well as COPD extends to all divisions of respiratory tract, parenchyma and blood vessels of the lung. As a result of chronic airway inflammation swelling of bronchial mucosa, mucus hyper secretion and bronchoconstriction are developed. These are coming out in airflow limitation (M. Roth, 2014). Thus, the inflammatory process plays an important role in the pathogenesis of BA and COPD. It is obvious that a pathogenic therapy must be directed equally towards elimination of chronic persistent inflammation and bronchospasm. To what fact do the modern recommendations attest?

Modern principles of therapy of COPD and BA and their faults.

As it is well known, in spite of a wide range of drugs for BA therapy, exacerbation of asthma, which requires hospitalization, can develop in any patient, regardless of the severity and duration of illness. The reasons for loss of control in BA and for need in hospitalizations mainly are inadequate basic therapy and / or poor patient adherence to compliance with daily recommendations and frequent administration of SABA (short-action $ß_2$-adrenergic agonists), which contributes to increasing of chronic inflammation and exacerbations. Regarding SABA, the frequent and long-term administration of thereof in prehospital phase is a risk factor for exacerbations, which provokes development of desensitization of adrenergic receptors. In addition, administration of these drugs more than 1-2 times a day, especially during the day time, is considered to be an argument for reconsideration of background therapy. The use of SABA over 200 doses per month is a lethality risk factor due to BA. In addition, the obverse case of SABA overuse is developing of electrolyte imbalances. Thus, the study of A.N. Nagdeote, Y.R. Pawade (2011) included 50 children with BA aged 2-12 years old. All children were examined at the treatment baseline. The treatment included Salbutamol and inhaled glucocorticosteroid (GC), at that, the latter was indicated to children with severe symptoms only. After 15 days of therapy, blood samples were taken again. The authors investigated the levels of potassium and sodium in plasma. The results showed that Salbutamol therapy contributed to a significant decrease in potassium levels in the blood of patients, regardless of the severity of BA. Sodium levels were not changed significantly. The results of the study are presented in Table 1.

Therefore, SABA therapy can significantly affect the electrolyte composition of blood plasma.

It should be noted that patients with chronic respiratory disorders have a background micronutrient deficiency, as confirmed in the study of Faris M. Ouf et al. (2015). This research with participation of 60 adult patients with COPD allowed identifying the background changes in plasma electrolyte composition in such patients. The authors note that patients with COPD have significant electrolyte imbalance even without treatment. The results of electrolyte levels measurements in patients with COPD prior to treatment are given in Table 2.

Dynamic pattern of electrolyte balance in the course of standard COPD treatment was also explored during the study. The authors concluded that the standard COPD therapy can lead to further strengthening of blood serum electrolyte composition. Moreover, electrolyte disorders are warnings of possible complications, and patients with significant variations in the levels of potassium, magnesium and chloride are at high risk group as to getting into Intensive Care Unit.

Thus, when assigning therapy for patients with BA and COPD at the hospital stage, one should be aware of a high probability of hypokalemia and hypomagnesemia in these patients, especially given the uncontrolled use of SABA.

The ways of optimization of hospital treatment of patients with BA and COPD

In general, for control of BA both in prehospital and hospital stage combination of GC / LABA (glucocorticoids / long-acting $ß_2$ agonists) is commonly used in SMART mode. According to the recommendations of GINA in case of deterioration due to desensitization of $ß_2$-adrenoreceptors, as well as reduction of sensitivity of patients to corticosteroids, patients with moderate and severe BA will need complex therapy of bronchospasm and chronic inflammation of the airways by means of second-line medicinal products, main effect direction of which is relief of bronchospasm (ipratropium bromide, tiotropium bromide, theophylline). Recommendations of GOLD, which contain the basic principles of COPD case management, also divide the treatment into two stages. At the hospital stage intravenous administration of second-line medicinal products is used mainly with broncholytic purposes in cases when the efficacy of GC and short-acting bronchial spasmolytics is insufficient. However, as it was noted above, at hospital stage the elimination of bronchospasm is not the only objective of the treatment of BA and COPD. Complex treatment with mandatory elimination of both inflammation and bronchospasm is a pathogenetically justified principle in the treatment of exacerbations. From this point of view medicinal products that are PDE inhibitors are especially noteworthy. Inhibitors of PDE with rational composition are able to provide such a complex treatment. But what does "rationality" stand for in this context? Let's try to understand. The need to prescribe PDE inhibitors in the hospital, as it has been described above, is conditioned by decreased sensitivity of $ß_2$-adrenoreceptors to SABA due to frequent administration of thereof in prehospital phase due to deterioration. Accumulation of cAMP by virtue of inhibition of the process of its transformation into adenosine monophosphate (AMP) is the basis of the mechanism of action of PDE inhibitors (fig.).

Accumulation of cAMP in the cells of unstriped muscles of bronchus leads to the relaxation of thereof and to broncholytic effect development. Anti-inflammatory effect of PDE inhibitor is being implemented due to the inhibition of the production of leukotrienes, IL, histamine, and tumor necrosis factor by the immune competent cells (neutrophils, T-lymphocytes, eosinophils, macrophages, mast cells). It is extremely important to note that inhibitors of PDE implement their effects fully only in terms of the presence in the body of many trace elements in concentrations close to normal. This is due to the fact that the main substrate is cAMP, which is responsible for the development of biological (medical) effect of PDE inhibitor, and it is formed from ATP. Reactions with formation of ATP as the result of glucose catabolism require normal content of essential trace substances, especially magnesium and potassium. In the case of deficiency of magnesium and potassium, reaction of ATP slows down. It is well known that magnesium is a catalyst of 6 of 9 reactions of glycolysis and is present in the cell in the form of compound with ATP (M. Faris, 2015), and is necessary for each reaction of Krebs cycle. In addition, magnesium activates adenylate cyclase, which controls the synthesis of cAMP. Potassium further activates pyruvate kinase which catalyzes glycolysis with formation of ATP. In addition, potassium activates the activity of enzyme systems involved in formation of ATP in the process of oxidative phosphorylation (V.I. Maltsev, V.K. Kazymyrko, 2015). Thus, for patients with BA and COPD with their background of lack of potassium and magnesium, one must include micro-elements for normalization of plasma electrolyte composition into the scheme of treatment with second line medicinal products. This will help to achieve the desired therapeutic effect of PDE inhibitors.

So pathogenetically substantiated scheme of therapy of BA and COPD at the hospital stage should include:

- effective relief of bronchospasm;
- reliable inflammation control.

It is a paradox but up until now for patients with acute exacerbation of BA and COPD at the hospital stage there are no drugs with comprehensive action which would neutralize both bronchospasm and inflammation presented on the market. **Derkast®, a new drug (Yuria-Pharm LLC, Ukraine) can become an example of a modern approach that takes into account the peculiarities of pathogenesis of BA and COPD exacerbation at the hospital stage.** It is the only parenteral PDE inhibitor for treatment of patients at the hospital stage which at the same time relieves from bronchospasm and inflammation during BA and COPD exacerbation due to the fact that the composition of this medicinal product is well-thought. By inhibiting PDE-3, PDE-4, PDE-5, Derkast® contributes to the development of broncholytic and anti-inflammatory effect. Potassium and magnesium ions that are part of medicinal product composition provide the desired therapeutic effect from implementation of PDE inhibitor. Derkast® is released in the form of prepared solution for intravenous infusion, which provides a prompt and controlled effect. It is necessary to emphasize one more time that Derkast® is a breakthrough medicinal product able to influence basic chains of pathogenesis of BA and COPD exacerbation.

There is no doubt that at present BA and COPD are the #1 problem of Pulmonology. Steady growth in prevalence, the high level of mortality (more than 3 million people die from BA and COPD annually!), the increase of the ratio of the weight of the heavy forms — these are the reasons that cause a high medical and social relevance of these diseases. It is important to note that main reasons of death of patients with BA and COPD for today are both absence of adequate long-term treatment and not timely and improper provision of emergency care. A comprehensive approach to hospital treatment of patients with BA and COPD using new medicinal product Derkast® is not just a pathogenetically reasonable mean for improving the treatment efficacy, but it is also a way to reduce mortality.

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Table 1. The levels of sodium and potassium in patients with BA on the background of Salbutamol therapy A.N. Nagdeote, Y.R. Pawade, 2011)

Plasma electrolytes	Before treatment	After 15 days of treatment
Sodium (mmol/l)	138±3.4	139±3.8
Potassium (mmol/l)	4.13±0.46	3.6±0.42

Table 2. Changes of plasma electrolyte composition in patients with COPD (Faris M. Ouf et al. (2015)

Plasma electrolytes	Patients with COPD	Control group
Potassium (mmol/l)	3.28±0.54	4.49±0.33
Sodium (mmol/l)	132.40±4.88	142.40±3.08
Calcium (mmol/l)	1.08±0.28	1.23±0.09
Magnesium (mmol/l)	1.85±0.17	2.20±0.14
Chloride (mmol/l)	84.75±7.31	100.30±2.67

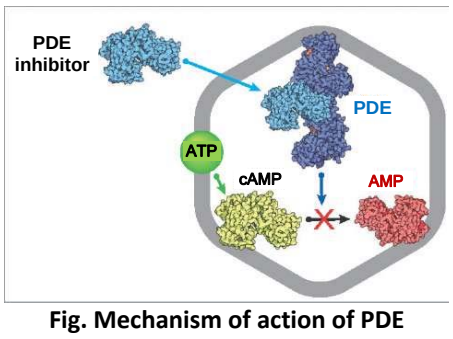

Fig. Mechanism of action of PDE inhibitors

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.