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Tiotropium bromide (spiriva) – efficacy, feasibility, relevancy in COPD

Key words: *COPD, cholinolytics, tiotropium bromide.*

In the recent years, the study of development and progressing peculiarities of socially important diseases becomes increasingly important. It should be mentioned that among bronchopulmonary system diseases, such pathology as chronic obstructive pulmonary disease (COPD) occupies one of the leading positions. In the last decades, tobacco smoking, adverse social and living conditions, increased number of patients with genetic determination of respiratory system diseases, and atmospheric contamination from automobile transport and industrial emissions combined with impaired barrier function of mucous membranes of respiratory system and impaired mechanism of immune protection caused a burst-type increase of COPD rate. According to the data of World Health Organization (WHO), mortality from COPD increases throughout the world, and it is expected that by 2020, it achieves 6 million of patients a year, occupying the same level in the structure of causes of death with such diseases as CVDs, traumas due to traffic accidents and brain vascular diseases [1].

COPD is one of the major healthcare challenges, primarily, due to its high rate among employable population, constant persistent progressing, often in combination with other pulmonary pathologies and aggravating effects of other concomitant diseases. In terms of the global society, COPD causes great social and economic losses. Thus, as stated by Yu.I. Feshchenko, Doctor of Medicine, Professor of the National Academy of Medical Sciences of Ukraine, no one has ever estimated financial losses from COPD in Ukraine, however, e.g., in the USA, this amount is about USD 780 million per year.

Principal pathologic syndrome in COPD is a bronchial obstruction characterized by obstructed airflow in respiration, and is assessed by a patient as dyspnea. Additionally to subjective signs (dyspnea, chest tightness), bronchial obstruction is assessed by spirometric data, for which reduced velocity parameters are common (forced expiratory volume 1-second (FEV_1), and peak expiratory flow rate (PEFR)). However, the earliest sign of bronchial obstruction, even at high FEV_1, is the reduction of FEV_1/PEFR <70 %.

It is known that bronchial obstruction in chronic pathology of respiratory organs includes functional (reversible) and organic (non-reversible) components [2]. If the former ones (bronchial spasm, bronchial mucosa edema and mucous hypersecretion) may be subject to reverse development under the effect of treatment, the latter ones (peribronchial fibrosis and pulmonary emphysema) are defined by marked changes of tissue structure and may not be resolved spontaneously or therapeutically.

Medication therapy of COPD is intended to prevent and control the symptoms, and to reduce the rate and severity of exacerbations, improvement of health condition and tolerability of physical exercises and life quality of a patient. The most efficient way of administration of medicines is an inhalation through direct supply of medications into the bronchi and the onset of their action. Furthermore, high concentrations of medicines in respiratory tract are formed, and their concentrations in blood remain negligible. Basic therapy should comply with the following principles:

- regularity and stability of basic therapy;
- gradual treatment intensity increase depending on the severity and stage of disease;
- the need of regular monitoring of individual response to the treatment.

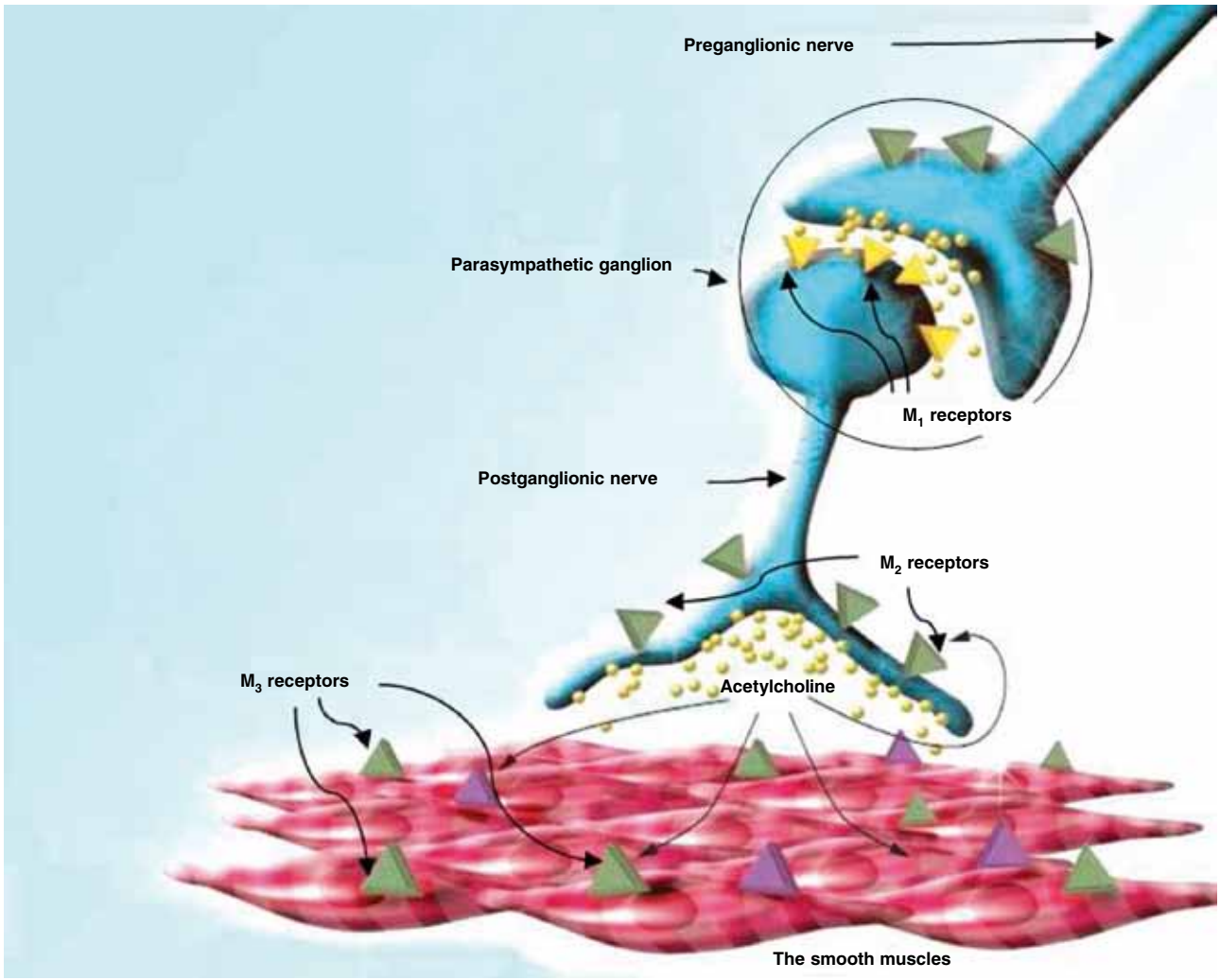

Fig. 1. **Localization of various muscarinic receptor subtypes (adapted from Peter J. Barnes, Expert Rev Resp Med, 2012).**

Increased resistance of respiratory tract due to spasm of smooth musculature is one of the main causes of development and aggravation of COPD symptoms, due to this, elimination of bronchial obstruction in COPD is ensured by the effect on its reversible component. Regardless the difference in the mechanism of action of other bronchodilators, its main property is the ability to reduce the spasm of smooth muscles of bronchi and to facilitate airflow in the lungs. Today, COPD treatment is performed using predominantly three groups of modern drug products – cholinolytics, β^2-agonists and inhalation GCSs.

Considering the statement of Peter. J. Barnes, a famous scientist, «COPD is a disease, when an increased cholinergic tone either may or may not be a single reversible component», practitioners should always keep in mind the presence of cholinolytics in their medical toolkit that are able to control the course of this disease, reduce the rate and severity of exacerbations. One of the most efficient cholinolytics of those present in all recommendations for long-term therapy of COPD patients is tiotropium bromide. In fact, due to tiotropium bromide, the group of prolonged-acting cholinolytics was included to all orders and regulations in the global scale.

Considerable advantage of the given drug product group is the lack of cardiotoxic effect, which makes it possible to use them in patients with circulatory and cardiac impairments, which are usually associated with the given disease. Furthermore, susceptibility of bronchial M-choline receptors is not reduced with age, and this is specifically important, as this makes it possible to use cholinolytics in elderlies and old-age patients. Specifics of tiotropium bromide ensure its use in wide range of bronchopulmonary pathology, and due to its easiness and availability of an inhalation device, it occupies a specific place in pulmonology practice.

In respiratory tract of humans, parasympathetic nervous system consists of vagus nerve branches, which accompany the bronchial tree throughout its length (Fig. 1). This is the vagus bronchomotor tone that strategically determines the condition of smooth muscles of respiratory tract, and therefore, an important factor determining the lumen of respiratory tract [3]. Cholinergic innervation is most common at the level of large- and medium-caliber bronchi, and to a lesser extent, at the level of peripheral bronchi. Endogenic neurotransmitter of cholinergic nerve endings is acetylcholine, and its action is determined by nicotine and muscarinic cholinergic receptors.

Muscarinic receptors are found mainly on effector cells receiving innervation from postganglionic parasympathetic nerves. Minimum 5 subtypes of muscarinic receptors are

known [3]. M1 receptors are located in peribronchial ganglions, and their stimulation facilitates signal transmission from pre- to postsynaptic fibers. M2 receptors are localized on postganglionic nerve fibers, and M3 receptors are found on effector cells (smooth muscles, secretor cells). Through M1 and M3 receptors, bronchoconstriction effect of parasympathetic nerve system is realized, and stimulation of secretion in tracheobronchial glands.

Thus, as opined by most domestic and foreign scientists, an ideal anticholinergic agent should inhibit both M1 and M3 receptors. Today, such drug mediators include tiotropium bromide, a choline-blocking agent with an effect about 10-fold of that observed in its precursor ipratropium bromide.

To our opinion, specific attention should be paid to the data on therapeutic effect of prolonged M-cholinolytic tiotropium upon exacerbation rate of chronic obstructive pulmonary disease, which is assessed as complication of pathology course. UPLIFT (Understanding Potential Long-term Impacts on Function with Tiotropium) results demonstrated that tiotropium prolongs remission period at the average to 4,1 months ($p<0,001$), considerably reduces the disease exacerbation rate in equivalent to patient-years. Furthermore, the same study demonstrated significant improvement of life quality in a four-year observation as indicated by the data of St. George's Respiratory Questionnaire, i.e., by 3,63 points [4].

As indicated by the data from publications of M. Decramer et al. (2008), tiotropium used concomitantly with other bronchodilators and inhalation glucocorticosteroids ensures further significant reduction of exacerbation rate by 14 % and prolongs the time to first exacerbation to 16,7 months vs. 12,5 months in control group [5]. Furthermore, tiotropium significantly reduces the risk of disease exacerbation with subsequent hospitalization. As shown by the results of UPLIFT study, tiotropium (Spiriva®) in the treatment of COPD patients demonstrated improved efficacy in terms of pulmonary function and safety of prolonged use [6]. UPLIFT is one of the most large-scale COPD studies among 5993 COPD patients from 37 countries of the world. For 4 years, patients receiving tiotropium reported of their life quality improvement as compared with study baseline. Within the period of study, patients from tiotropium group reported reduced mortality risk by 16%. It had been determined that positive effect of tiotropium therapy upon survival, even following inclusion of death cases reported upon the drug product discontinuation into the analysis.

Vogelmeier C. et al. (2011) in a large-scale one-year study POET-COPD compared long-term efficacy of tiotropium and salmeterol, with the principal objective to assess prophylactic effect of both drug products in terms of exacerbation rate in COPD patients. Study results demonstrated that tiotropium therapy vs. salmeterol ensured a longer period to any first exacerbation (187 vs. 145 days), and increased time to the first severe exacerbation with 28 % risk reduction. Furthermore, tiotropium also reduced the annual rate of severe exacerbations by 27 % [7].

A retrospective study (Short P.M. et al., 2012) using the database of the NHS National Services Scotland demonstrated that tiotropium used concomitantly with inhalation corticosteroids and long-acting β^2-agonists ensured all-cause mortality reduction by 35 %, hospitalization rate reduction by 15 % and reduced use of oral corticosteroids by 29 % as compared with double inhalation corticosteroid and long-acting β^2-agonists therapy [8].

Cholinolytics as competitive acetylcholine antagonists block muscarinic receptors in the bronchi, prevent and inhibit bronchial obstruction caused by vagus nerve tone increase [9]. Furthermore, selective M-cholinolytics are able to block the reflectory bronchial spasm arising due to the effect of irritants (dust, resin etc.) and reduce mucus hypersecretion by bronchial glands [10]. As indicated by many renowned contemporary scientists, cholinolytics render specific anti-inflammatory effects. Pleiotropic nature of pharmacodynamic and pharmacokinetic effects of tiotropium bromide ensures reduction of respiratory tract inflammation signs and their colonization by pathogens; improvement of bronchial flow; reduces mucus secretion by mucous glands and goblet cells [11].

All these data mentioned above speak in favor to the use of tiotropium bromide in the first-line therapy of chronic obstructive pulmonary disease.

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ТИОТРОПИЯ БРОМИД – ЭФФЕКТИВНОСТЬ, РАЗУМНОСТЬ, НУЖНОСТЬ ПРИМЕНЕНИЯ ПРИ ЛЕЧЕНИИ ХРОНИЧЕСКОГО ОБСТРУКТИВНОГО ЗАБОЛЕВАНИЯ ЛЕГКИХ

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Резюме

Хроническое обструктивное заболевание легких (ХОЗЛ) – одна из основных проблем здравоохранения, в первую очередь – в результате его широкого распространения среди трудоспособного населения, постоянного неуклонного прогрессирования, частого сочетания с другой патологией легких и тягостного влияния на другие сопутствующие заболевания. Основным патологическим синдромом при ХОЗЛ является обструкция, характеризующееся ограничением воздушного потока при дыхании и оценивается больным как одышка. Врачам-практикам следует всегда помнить о наличии в медицинском арсенале холинолитиков, которые блокируют мускариновые рецепторы в бронхах, предупреждают и подавляют бронхообструкции, вызванную повышением тонуса блуждающего нерва. Одним из самых эффективных холинолитиков из тех, что присутствуют во всех рекомендациях для длительного лечения больных ХОЗЛ, является тиотропия бромид. Собственно, благодаря препаратам тиотропия бромида группа пролонгированных холинолитиков и попала во все приказы и руководства мирового масштаба по лечению ХОЗЛ.

Ключевые слова: *ХОЗЛ, холинолитики, тиотропия бромид.*

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TIOTROPIUM – EFFICIENCY, REASONABLE, USEFULNESS IN THE TREATMENT OF COPD

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Summary

COPD is one of the major healthcare challenges, primarily, due to its high rate among employable population, constant persistent progressing, often in combination with other pulmonary pathologies and aggravating effects of other concomitant diseases. Principal pathologic syndrome in COPD is a bronchial obstruction characterized by obstructed airflow in respiration, and is assessed by a patient as dyspnea. Practitioners should always keep in mind the presence of cholinolytics in their medical toolkit, which block muscarinic receptors in the bronchi, prevent and inhibit bronchial obstruction caused by vagus nerve tone increase. One of the most efficient cholinolytics of those present in all recommendations for long-term therapy of COPD patients is tiotropium bromide. In fact, due to tiotropium bromide, the group of prolonged-acting cholinolytics was included to all orders and regulations in the global scale.

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