Review Article

Treatment of Patients Suffering from Exercise-induced Asthma: Prevention of Exercise-induced Bronchial Spasm – Literature Review

Leonid Oleksijovych Bezrukov, Olena Kostiantynivna Koloskova, Lorina Alimivna Ivanova, Tetiana Mykhailivna Bilous, Olena Grygorivna Grygola, Yuliia Igorivna Voitkevich[1]

Departments of Paediatrics and Children Infectious Diseases and [1]Internal Medicine, Clinical Pharmacology and Occupational Deseases, Higher State Educational Establishment of Ukraine "Bukovinian State Medical University", Chernivtsi, Ukraine

Abstract

Exercise-induced bronchial asthma (EIBA) or exercise-induced bronchial spasm is all terms that describe the phenomenon of transient obstruction of the bronchi after intensive physical stress. This article presents the recommendations about the rational administration of pharmacological and nonpharmacological methods of treatment of EIBA that in the majority of cases enables to provide considerable control over the disease without limitation of the physical activity of patients.

Keywords: Children, exercise-induced bronchial asthma, treatment

Introduction

In recent 50 years, a real boom has been noticed concerning the phenomenon of exercise-induced bronchial spasm (EIBS) in patients with bronchial asthma (BA) and individuals without this disease. The studies in this field have resulted in the determination of the major pathogenic links of this widely spread syndrome and substantiation of the methods of its prevention and treatment from the point of view of evidence-based medicine.[1] Especially great progress is achieved in the field of pharmacological management of patients suffering from exercise-induced BA (EIBA). The basic principle of this management in the majority of patients with BA is the administration of anti-inflammatory treatment by means of inhalation glucocorticosteroids (IGCS) and only in rare cases of EIBS – indication of β2-agonists inhalations of a short-term action directly before the physical exercise. A fundamental role of β2-agonists of a long-term action is considered as a supplement to the inhalation therapy with glucocorticosteroids and less commonly as a preventive measure of EIBS in cases when physical exercise is longer than 90–120 min. In case this treatment does not control EIBS occurrence, to prevent it leukotriene receptor antagonists, hormones, less commonly – muscarine receptor antagonists, and theophylline are prescribed before physical activity. In case of association of EIBA with anaphylaxis signs, antihistamines are indicated for such patients. β2-agonists of a short-term action are indicated to terminate EIBS occurrence. Therefore, in the treatment of EIBS as other phenotypes of BA, pharmacological therapy is directed to EIBS prevention (controlling therapy) and its termination (quick-response therapy). It should be noted that if BA is controlled the risk of EIBS occurrence considerably decreases, and due to this fact that the basic therapy is the main principle of pharmacological management of this BA phenotype enabling the patients to practice normal physical activity and even go for sport.[2] At the same time, it should be noted that EIBA treatment should be of an individual character, and the doctor must be completely aware of medicines used for pharmacological management of such

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Address for correspondence: Dr. Tetiana Mykhailivna Bilous, Department of Paediatrics and Children Infectious Diseases, Higher State Educational Establishment of Ukraine "Bukovinian State Medical University", Teatralna Square, 2, Chernivtsi 58002, Ukraine.
E-mail: bilous.tetiana@bsmu.edu.ua

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patients. Clinical description of the main drugs used for the treatment of EIBA is presented lower.

Inhalation β2-agonists (for a quick action – salbutamol and terbutaline and for a long-term action – formoterol and salmeterol): the prevention of EIBS in the majority of cases is achieved by the administration of inhalation β2-agonists of a quick action for the patients. These drugs prevent the development of bronchial spasm at the expense of blocking of proinflammatory mediators excretion by mast cells, and prevention of smooth muscles contraction under the action of such agonists as histamine, leukotriene, and prostaglandin E2.[3-5] At the same time, one should keep in mind that inhalations of β2-agonists of a short-term action do not eliminate inflammation of the bronchi which is considered to be the main cause of EIBS development in patients with BA. Moreover, everyday use of these drugs quickly results in the reduction of their positive effect at the expense of tachyphylaxis development.[6] Tolerance to β2-agonists is likely to occur due to a reduced number of β2-receptors on the surface of the mast cells which is usually restored after withdrawal of these drugs in an average 72 h later.[7,8] Tolerance is manifested clinically by a shorter term of action, longer period of renewal of the bronchial patency, and the necessity of more frequent administration of these drugs in increasing doses. Eventually, EIBA with everyday use of β2-agonists can be more severe and administration of these drugs for giving urgent aid has become less effective. It should be kept in mind that tolerance development to β2-agonists can be prevented by their use no more than 2–3 times a week with advisable interval of 72 h (irrespective of the fact whether they are administered alone or in combination with IGCS).[9]

Since the effect of inhalation β2-agonists of a short-term action begins 5–20 min later and continues from 2 to 4 h, in case of EIBA or with the aim to prevent EIBS of a longtermaction β2-agonists a reccomended by the patients for positive effect in an average during 12 h. Formoterol is a drug of choice in this case possessing a quick onset of bronchial protector and bronchial dilation action. On the contrary, a positive effect after salmeterol inhalation becomes 15 and 30 min later.[10,11] At the same time, it should be kept in mind that β2-agonists of a long-term action in case of everyday use alone or in combination with IGCS as well as β2-agonists of a quick action can lead to tachyphylaxis, and as a result – to more severe course of EIBA.[12,13] Development of tolerance to β2-agonists is accompanied by an increased release of proinflammatory mediators by mast cells and more pronounced bronchial constriction.[7] It is likely associated with the fact that in case of development of tolerance to β2-agonists simultaneous activation of receptors to leukotriene, histamine, and thromboxane occurs as well as involvement of cholinergic agonists into pathological process.[14,15] Considering the possibility of tolerance development to β2-agonists, their intermittent use is recommended avoiding their administration in the course of monotherapy.[16,17]

Taking into account the fact that physical exercise in children is often unpredictable by the time of its exposition to eliminate the risk of EIBS salmeterol can be taken in the morning or before going to bed.[18] Certain authors indicate that intermittent intake of salmeterol (50 mcg/day) in 22 h not only decreases the risk of EIBS development but also improves a basic function of the lungs in the morning. This protective effect of salmeterol was not absolute; however, it was found in 16 out of 23 children aged from 8 to 16. Another β2-agonist of long-term action formoterol is of a certain interest of clinicians not only due to its quick onset of action but also due to the fact that it does not possess doping property and can be used to prevent EIBS in sportsmen, especially in case of performing a prolonged physical load.[19] At the same time, it should be kept in mind, that inhalations of β2-agonists effective for the prevention and treatment of EIBS do not possess an expressive anti-inflammatory effect and do not eliminate the main cause of EIBA – inflammation of the bronchi. Their uncontrolled intake can promote the illusion of improvement and eventually result in uncontrolled course of the disease.[20]

Children who regularly go for sport requiring every day or several trainings a week, and those with an active way of life may experience behavioral dilemma: frequent physical load requires often intake of β2-agonists, leading to intensification of EIBA severity and more pronounced EIBS, which in their turn requires more frequent administration of these drugs in constantly increasing doses. The basic therapy with IGCS enables to break this vicious circle to some extent, although IGCSs do not prevent the development of tolerance to β2-agonists. They decrease EIBA severity and in this way promote the reduced need to take β2-agonists. It is important to know that IGCSs are required continuously but not intermittently together with inhalations of β2-agonists. Such an approach in the treatment of EIBA has appeared to be so much effective that a part of sportsmen with BA during summer Olympic Games took the combination of inhalation β2-agonists with IGCS has increased from 46.1% in 1996 to 87.2% in 2008. Since 2004, all the athletes took formoterol contrary to salmeterol as a kind of monotherapy.[21]

Administration of IGCS for the patients with BA enables to achieve control over the disease, although it excludes the indication of other short-term preventive drugs combined.[22,23] A positive effect of IGCS on EIBA and EIBS is initiated 4 h after the first dose and is of dose-dependent and time-dependent character.[24] In an average, the first plateau of efficacy is found in 1 week after the treatment with IGCS, and several months later – the second plateau. In general, the efficacy of IGCS in case of EIBA is from 30% to 60%, and it varies from a "complete" control to the minimal one. A certain group of patients with absent effect of IGCS remains a special subpopulation which is likely to depend on other factors.[25] It is indicated that inpatients suffering from EIBA, a control over the disease is achieved by means of the combination of IGCS and β2-agonists of a long-term action, withdrawal from the latter does not lead to intensification of EIBS.[26] Contrary

to this, it is evidenced that IGCS action on hypersensitivity of the bronchi to direct bronchospasmogenic stimuli is time-dependent and dose-dependent, while it is not found concerning EIBS. On this basis, the authors suggest different mechanism of a protective action of IGCS on the effect of direct and physiological stimuli. This conclusion was drawn after the examination of 37 BA patients aged from 6 to 14 who received fluticasone inhalations in the dose of 100–250 mcg/day during 4 months. Fluticasone effect concerning EIBS decrease was not found to depend on the dose of the drug and duration of its intake. On the contrary, the sensitivity of the bronchi to methacholine inhalations decreases both in case of increased doses of fluticasone and the duration of its intake. Opposite to the data presented[27,28] dose-dependent protective effect was not found concerning EIBS as well as concerning reduced content of nitrogen oxide in the expired air. Thus, after the treatment of 25 children with BA aged 5–14 years during 4 weeks by means of beclomethasone dipropionate inhalations in the dose of 50 mcg/day, forced expiratory volume in 1 s (FEV1) after physical exercise goes down 20.8% and the content of nitrogen monoxide in the expiratory air is 9.3 ppb. When this drug is indicated in the dose of 100 mcg/day, these indices are 20.9% ($P > 0.05$) and 8.9 ppb ($P > 0.05$), respectively.

Patients with EIBA with uncontrolled EIBS by means of monotherapy with β2-agonists or those treated with IGCS who require their frequent use are recommended to take leukotriene receptor antagonists every day (montelukast, zafirlukast, and cinalukast). The combination of montelukast with budesonide inhalation in the dose of 400 mcg was found to decrease EIBS signs significantly even at the end of the 1st week of treatment as well as bronchial sensitivity to mannitol in children with BA.[29] A protective effect of montelukast concerning EIBS starts 1 h after its intake, lasts for 24 h and does not result in tachyphylaxis in case of its long administration.[30,31] This characteristic of leukotriene receptor antagonists makes them rather advisable in the prevention of EIBS when children are not able to inhale β2-agonists or they cause side effects.[32] Since everyday treatment by means of leukotriene receptor antagonists promotes the development of tachyphylaxis, they can be administered for intermittent or basic prevention of EIBS, although their protective effect can be incomplete and they do not lead to deobstruction of the bronchi in case of exacerbation of EIBA.[33] Frequency and expressiveness of a protective action of leukotriene receptor antagonists concerning EIBS range widely in patients with EIBA from 30% to 80%.[34,35] In spite of the fact that these drugs do not possess bronchodilating effect, they accelerate the time of EIBS elimination in the process of quick-relieving treatment.[36] In general, variability of a protective effect of leukotriene receptor antagonists is likely to suggest the availability of a special subpopulation of patients with EIBA who are defined by the availability or lack of therapeutic effect as in case of other kinds of BA treatment.[37,38] On the whole, leukotriene receptor antagonists without their expressive side effects and development of tachyphylaxis can be administered for the single prevention of EIBS and in the process of urgent aid given to patients with EIBA.[39]

Stabilizers of mast cells (cromolyn sodium and nedocromil) in case of their inhalation directly before the physical exercise in patients with BA possess a short-term protective effect concerning EIBS occurrence, although they do not demonstrate bronchodilating action.[40,41] Usually, a protective effect concerning EIBS comes quickly; however, it lasts only 1–2 h and is dose-dependent. It is an interesting fact that the preventive effect of nedocromil sodium is as higher as more expressed EIBS.[42]

Anticholinergic Drugs (Ipratropium Bromide, Tiotropium Bromide)

Muscarinic receptor antagonists are recommended to be administered for the patients with EIBA in those cases when EIBS occurs irrespective of inhalations of β2-agonists or when there is a need in their frequent everyday use. A preventive effect of anticholinergic drugs concerning EIBS development is changeable and is connected with the block of bronchospasmogenic vagus action in combination with other bronchoconstrictor mediators.[43] A protective effect of these drugs is considerably weaker than in β2-agonists and stabilizers of mast cells. Thus, if administration of mast cells stabilizers decreases EIBS to 9,4%, the use of muscarine receptor antagonists decreases FEV1 after physical exercise only to 16% with an average difference value 6,6% (95% confidence interval: 1.0–12.2).[44] At the same time, considering bronchodilating action of these drugs, they are recommended to give urgent aid in case of EIBA exacerbation usually together with β2-agonists.

Antihistamines, Theophylline, and Other Pharmacological Agents

Antihistamines are recommended for patients with EIBA in those cases when comorbid atopic diseases are found, and inhalations of β2-agonists do not prevent EIBS development, or when they should be taken every day or frequently to achieve a preventive effect. Antagonists of H1-receptors are considered to possess a changeable effect concerning EIBS prevention, which is likely to be caused by the fact that histamine is the only one out of three important mediators of bronchial spasm in patients with BA.[45,46] These drugs are considered only to decrease the signs of EIBS but not to protect against them. Thus, the administration of loratadine in the daily dose 10 mg during 3 days for 14 patients with EIBA aged 7–17 years demonstrates considerable decrease of FEV1 after graduated exercise concerning placebo at the 2, 5, 10, 15, and 30 min ($P < 0.05$). Although, the mean value of FEV1 drop at the 5th min of these patients reaches 15%, as compared to the initial one.[47] Although the treatment of concomitant allergic rhinitis by means of topical IGCS is likely to relieve the course of EIBA, the administration of

loratadine for these patients does not considerably affect the development of EIBS.[48]

Theophylline and aminophylline are recommended to be taken only in the combination of the basic controlling therapy of EIBA. Thus, the studies conducted at the end of the last century showed that their preventive effect concerning EIBS is less than doubtful.[49]

It should be noted that in the process of studying pathogenesis of EIBS in patients with BA and those without the disease the effect of many pharmacological agents on the development of this clinical phenomenon was investigated. In certain patients, calcium channel blockers, furosemide, antagonists of α-adrenergic receptors, inhalations of low molecular heparin, and hyaluronic acid are found to possess a protective effect concerning EIBS.[50,51] It should be noted that all of them are not recommended for clinical use as pharmacological agents to prevent EIBS due to their doubtful effect and their action in multicomponent pathogenesis of EIBA.

To prevent EIBS in patients with EIBA in addition to the above-mentioned drugs, nonpharmacological methods of treatment are usually recommended. They include recommendations directed to the prevention of trigger stimuli associated with physical exercise (dry and cold air, pollutants, and oral breathing). The preliminary stage of exercises before physical load also possesses a preventive effect under conditions excluding cooling the respiratory tract promoting the development of refractory period during 1–4 h.[52,53] It should be noted that all these recommendations do not suggest refusal from pharmacological treatment since the combination of the mentioned therapeutic methods increases its efficacy considerably.[54] The risk of EIBS development and its clinical signs decreases to some extent due to the modification of diet at the expense of its enrichment with omega-3 polyunsaturated fatty acids, Vitamin C, lycopene, and restriction of table salt intake.[55,56]

In general, the above-mentioned treatment of EIBA from the positions of evidence-based medicine can be represented in the form of the following recommendations:[17,57] β2-agonists of a short-term action should be indicated for patients with EIBS 15 min before physical load (validity level A). In case of every day or more frequent administration of β2-agonists, the course of treatment is supplemented with the drugs of a controlling action: IGCS (every day no <2–4 weeks) – average validity level B; stabilizers of mast cells before physical load (validity level A); inhalations of anticholinergic drugs (low validity level C); and antihistamines are indicated for patients with concomitant atopic diseases (validity level B).

Recommendations for all the patients with EIBA: Exclude cooling of the respiratory tract in the period before main physical load (validity level B); a routine application of a mask or warming with moistened air – for all the patients who experience physical load as a trigger under conditions of cold weather (validity level C); and diet correction at the expense of restriction of table salt intake (validity level B), enrichment with cod-liver oil (validity level C), enrichment with lycopene (validity level C), and enrichment with ascorbic acid (validity level B).

Conclusions

The above recommendations enable to consider that treatment of EIBA is two-sided and included controlling therapy of BA and prevention of EIBS. In addition, it should be noted that in the period of exacerbation patients are supposed to get quick-relieve therapy that sometimes can be complicated by exercise-induced anaphylaxis.[58,59] Analysis of the above recommendations and their discussion give the basis to consider that a rational administration of pharmacological and nonpharmacological methods of treatment of EIBA in the majority of cases enables to provide considerable control over the disease without limitation of physical activity of patients. At the same time, it should be admitted that pathogenesis of this phenotype of BA is not sufficiently studied. It is reflected in unsolved issues of diagnostics and the treatment of EIBA in childhood.

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Conflicts of interest

There are no conflicts of interest.

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