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Means of drug delivery in the event of inhalation therapy in children: selection criteria

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Article received: 24.03.2014. Accepted for publication: 17.09.2014.

Inhalation therapy as means of drug delivery is a key aspect of therapy of respiratory diseases in children, which plays an important role in achieving control over bronchial asthma. Optimal clinical effect requires comprehensive selection of inhalation devices given the drug's peculiarities, the child's age, severity of his/her condition, the patient's cognitive potential and capabilities of his/her parents, as well as clinical recommendations on the corresponding diseases. It is rather important to observe individual approach and the patient's preferences in order to ensure adherence to the recommendations. One of the crucial conditions of effective inhalation therapy is a clear explanation of the inhalation technique and device maintenance by the doctor, as well as regular medical control over observation of the given instructions by the patient and his/her parents. The article presents an algorithm of selecting means of inhalation drug delivery for use in children and the review of currently marketed inhalers, their advantages and drawbacks.
Keywords: *children, inhalation therapy, asthma, metered aerosol inhalers, metered powder inhalers, nebulizers, Easyhaler.*

Introduction

Inhalation therapy for children has been gaining significance in the recent years. Direct drug delivery to the airways in pediatric clinical practice is especially important for patients with bronchopulmonary diseases, such as bronchial asthma, mucoviscidosis, bronchopulmonary dysplasia, primary ciliary dyskinesia, congenital malformations of trachea and bronchi, neuromuscular diseases, stenosing laryngotracheitis (croup) and atelectases [1].
5 main factors are to be considered for inhalation therapy to have a desirable effect:
- disease etiology;
- drug peculiarities;
- required drug pulmonary deposition level;
- type of inhaler;
- patient's capabilities.

Thus, doctors ought to adequately assess severity and pathophysiological aspects of the patient's disease, the drug's pharmacological peculiarities and how these parameters may affect the drug's pulmonary deposition. Inhaler selection is also important; it ought to be based on the first three factors, as well as capabilities of the patient and/or the parents thereof – both physical and, in some cases, financial [1].

Drug delivery systems

Studies of healthy volunteers demonstrated that the optimal particle size for successful inhalation into the lower airways is 1-5 mcm [2]. However, in the event of severe airway obstruction, e.g., at mucoviscidosis, the deposition pattern may not be that homogenous, so most of the drug will be delivered not to peripheral, but to central segments. An extremely small number of studies touching upon inhalation drug deposition in infants has to be taken into consideration, as there are only assumptions that the respirable aerosol fraction therein might be represented by smaller-sized particles, as in patients with pronounced obstructive ventilation disorders [1].
It goes without saying that almost all inhalation drug delivery systems have initially been developed and tested on adult patients, which is why specific characteristics of infants have not always been taken into account.
Various drug delivery systems are now available for doctors: nebulizers, metered aerosol (MAIs) and metered powder inhalers (MPIs) [3-6].
Wide variety of inhalation drug delivery systems is often seen as a serious challenge by doctors: what type of inhalers is preferable in each case?
Meta-analysis of 24 studies, including 3 studies involving pediatric patients, indicates that inhaler effectiveness is comparable in the event of thorough observation of the appropriate instructions for use [6, 7]. Current guidelines on bronchial asthma also help doctors significantly [3, 8-13]. Moreover, in 2011 the European Respiratory Society (ERS) and the International Society for Aerosols in Medicine (ISAM) published a detailed report on the inhalers for respiratory pathologies available at that time: “What the pulmonary specialist should know about the new inhalation therapies” [14].
According to the aforementioned guidelines, doctors ought to:
1) select an inhaler accordingly with the patient’s age;
2) recommend using MAIs with spacers or nebulizers equipped with facepieces to under-3 children;
3) teach children of 3-6 years of age inhalation using a mouthpiece, if they perform the inhalation technique properly;
4) teach over-6 children proper technique of inhalation using MPIs and MAIs;
5) check if the patient performs the selected device’s inhalation technique properly.

Inhaler selection largely depends on the drug’s peculiarities: e.g., not all drugs feature pharmaceutical forms compatible with MAIs and MPIs or are produced in a liquid form for inhalation with a nebulizer (pic. 1).

Nebulizer

Nebulizer was invented in 1858 by J. Sales-Gyrons; it is considered to be the first device for inhalation therapy [15]. The most widely used are compressor nebulizers; however, membrane (electronic mesh) nebulizers have recently entered the market [4, 5, 16]. There are also ultrasonic inhalers, the use whereof for diseases of lower airways is limited, as heating of the aerosol-generating piezoelectric crystal results in heating and sometimes even destruction of a range of drugs containing protein components, dornase alfa in particular [17, 18]. Moreover, ultrasonic inhalers are incapable of adequate nebulization of suspensions, which is especially important in the case of glucocorticosteroids [4, 5, 19], and viscous fluids, which is important for antibacterial drugs [1]. In addition, it ought to be mentioned that many nebulizers are equipped with a facepiece recommended for inhalation to under-2 children and in the event of emergency therapy.
Nebulizer advantages are, without any doubt, additional airway humidification and lack of need in coordinating the respiratory manoeuver with drug release. Thus, nebulizers are devices of choice in infants and patients with severe respiratory disorders. However, considerable disadvantages of nebulizers are relatively large dimensions, need in an electric power source and, often, a rather high price. Amount of the drug delivered to the lower airways may decrease if a child cries and if the facepiece is not fit tight [12]. Moreover, use of a facepiece results in higher

drug loss and risk of eye contact [1]. Taking into consideration the aforementioned, doctors ought to strive for the use of mouthpieces from the youngest age possible; in most cases, they may be utilized in the children as young as 3 years [12].
Despite a long history of nebulizer use, drug delivery with these devices has not been standardized. The European recommendations request manufacturers of nebulizer therapy drugs to register such drugs for use with certain types of inhalers [20]. However, this request has not been made obligatory [1], which is why it is often infeasible to completely accurately predict both therapeutic and toxic effects of the nebulizer-delivered drugs [1].
Proper regular nebulizer disinfection is often a challenge as well. Thus, a study of patients with mucoviscidosis using nebulizers demonstrated that microbial contamination of the devices reached 55%; that fact was linked to failure to comply with instructions for the inhalers' hygiene [21]. According to the study performed by L.X. Brzezinski et al., who analyzed nebulizer contamination in 28 patients with mucoviscidosis, improper cleaning and disinfection of devices was observed in 22 cases (78.6%) [22]. Moreover, storage of an unpacked nebulizer domiciliary may lead to the device's contamination with allergens and lower therapy effectiveness in patients with bronchial asthma [23].
The Global Initiative for Asthma (GINA) recommends using almost all the available inhalers in children, thus granting doctors and patients the right to cooperative selection of a drug delivery device (see pic. 1) [8, 9].
The patient's cognitive potential ought to be taken into account for a child to receive an adequate dose of a prescribed drug, which is why MAIs with spacers or an appropriate facepiece ought to be used in infants. Alternatively, nebulizers with facepieces may be utilized.

Metered aerosol and metered powder inhalers

Systemic review published in 2006 indicates equivalent effectiveness of nebulizers and MAIs for non-severe asthma episodes. Moreover, MAIs preceded nebulizers in terms of clinical outcomes and the rate of side effects. The other positive factors of utilizing MAIs included lower risk of cross-infection and a possibility of using an individual delivery device [24].
Results of a clinical-economic study published in 2011 indicate advantage of administering Albuterol via MAIs with spacers over inhalations using nebulizers for moderate bronchial asthma exacerbations at emergency units both for the clinic and the patients' families [25]. This study also demonstrated that only 2 out of 10 pediatric emergency units in Canada routinely use metered aerosol inhalers despite extensive proof of broncholytic inhalation equivalence of MAIs with spacers and nebulizers. Nebulizers are also used broadly in emergency cases in Russia; however, it is rational to use MPIs or MAIs, recommended for use in an appropriate age group, after the condition has stabilized.
Successful use of MAIs with spacers requires maximum reduction of time between drug dose release and the patient's inhalation: aerosol particles deposit on spacer walls due to gravitation. Drug deposition on spacer walls may increase in the event of electrostatic stress of this plastic device's walls. Specific treatment of spacers or use of antistatic devices is recommended to alleviate this effect [12]. Please remember that small-sized spacers (less than 350 ml) are preferable for infants [8].
From the age of 4-6 years (depending on the drug's permitted age range and the child's ability to perform the inhalation technique properly), breath-actuated MPIs or MAIs may be used along with MAIs with spacers. There are over-6 children with difficulty using MAIs with spacers, most of whom are capable of a powerful breath required to use an MPI [26].
Metered powder inhalers are recommended by the Expert group of the ERS and ISAM specialists as an optimal therapy for the school-aged children unwilling to use a spacer and, therefore, receiving a smaller amount of drug than needed [14].
Effective inhalation using most MPIs requires a rather high breath rate (pic. 2); actually, this sets a significant problem only rarely, as 74% of the preschoolers and almost all the over-6 children are capable of a peak breath rate over 30 l/min. [27].

Adequate specialist's interaction with the patient (parents or legal representatives) is crucial for baseline therapy of bronchial asthma, as treatment usually lasts for a long term. At the same time, it was observed that insufficient cooperation of the patient (parents) is often caused by inappropriate use of the inhaler [8]. Thus, ease of use and the patient's preferences ought to be taken into consideration when selecting an inhaler. Continuous training of the patients (parents or legal representatives) regarding the inhalation technique and subsequent regular control at each visit to the hospital are required [3, 4, 8, 13].

Metered powder inhalers constitute a rather versatile group of devices single-dose capsule (Spinhaler, Aerolizer), multidose blister (Diskhaler with a Rotadisk), Diskus (Multidisk) and multidose reservoir inhalers (Easyhaler, Turbuhaler, Cyclohaler).

One of the easy-to-use and compact MPIs is multidose inhaler Easyhaler (Orion Corporation [Orion Pharma], Finland). 2 drugs have been registered in the Russian Federation: inhalation glucocorticosteroid Budesonide Easyhaler (200 mcg/dose, 200 doses) (Certificate of registration No. LS-002227 of 20.10.2011) and prolonged β_2-agonist Formoterol Easyhaler (12 mcg/dose, 120 doses) (Certificate of registration No. LS-002226 of 30.09.2011). The inhaler's construction enables formation of < 5 mcm outgoing particles and ensures the drug's optimal deposition in airways. Dose meter helps to control the process of treatment and serves as a notification for timely specialist visit planning.

The delivery device is designed in such a way that most patients encounter no difficulty using it; inhalation ensures a desirable clinical effect, which is why many specialists prefer Easyhalers. It has been proven by clinical studies of both adults and children [28-32].

A retrospective pharmacoeconomic study of outpatient budesonide administration by means of various MPIs to 6-80-years-old patients with asthma indicates that Easyhaler, along with other MPIs, ensures control achievement while featuring a better price-effectiveness ratio (75% probability) [33].

Conclusion

We would like to repeat that different inhalation drug delivery means ought to be prescribed to patients of different age.

Nebulizer inhalations are preferable for patients with poor inhalation coordination and ability to actuate an inhaler (infants, patients with severe lung pathology, including severe bronchial asthma exacerbation, and patients with very low cognitive potential).

In most cases, MAIs with spacers may be used in infants. There is no need in baseline nebulizer treatment of bronchial asthma in over-3 children as this delivery method has a range of the aforementioned limitations.

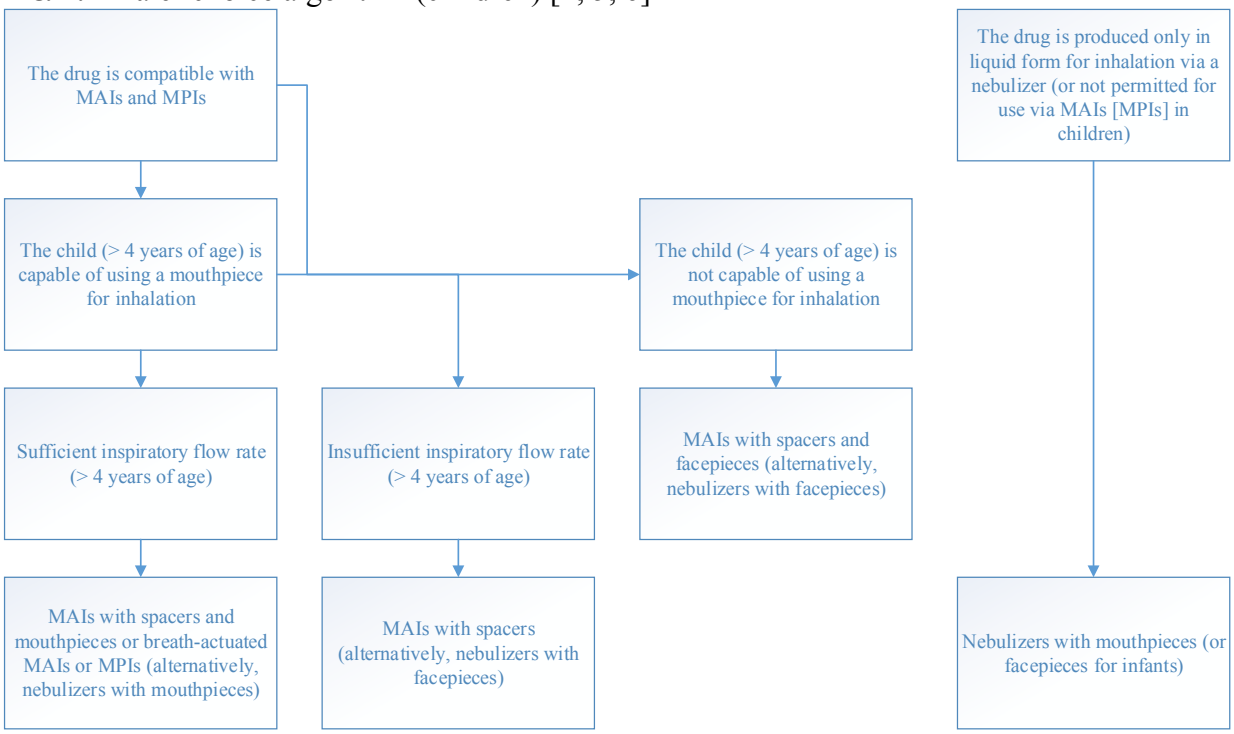
Children over 4-6 years of age are to be taught proper inhalation technique using portable delivery devices. Baseline therapy may be performed using MPIs and MAIs, including breath-actuated devices. An important aspect to consider when selecting an inhaler is that the easier and more comprehensible the inhalation technique is, the higher the patient's (and the parents' thereof) compliance and chance of achieving control over the disease.

Adequate selection of an inhaler for a child ought to be based on the recommendations given in the commonly accepted clinical guidelines and take individual peculiarities of patients and the parents thereof into consideration. Role of the doctor responsible for teaching the proper inhalation technique and subsequent regular control thereof is extremely important. Easyhaler is characterized by a convenient shape, ease of inhalation technique and optimal drug delivery to the lower airways; this makes use of Easyhalers possible in the children as young as 6 years.

CONFLICT OF INTEREST

The authors have indicated they have no financial relationships relevant to this article to disclose.

Pic. 1. Inhaler choice algorithm (children) [1, 5, 6]



Pic. 2. Inspiratory flow rate required for pulmonary drug delivery using a metered powder inhaler (MPI) [10]

MPI type	**Minimal inspiratory air flow rate required for pulmonary drug delivery, l/min.**
Turbuhaler	30 (optimal – 60 l/min.)
Novolizer	> 35
Diskus	30
Handihaler	30
Aerolizer	> 60
Easyhaler	28

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