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Aerosolotherapy in respiratory system diseases

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Summary:

Asthma, a chronic inflammatory disease of the respiratory system, is found worldwide among people in every age. Correct diagnosis of asthma is indispensable to proper pharmacological treatment. Correct therapy enables a decline of bronchial hyperresponsiveness and quick elimination of bronchial obturation. Drugs use in the treatment of asthma are divided into immediate (bronchodilatators, used in acute attacks), and day-today medicines with anti-inflammatory properties. A very important factor in treatment of asthma is a regular application of anti-inflammatory drugs, mainly inhalatory corticosteroids. Inhalatory way of drug application in treatment of aspiratory system diseases has the advantage over oral and parenteral administration, because it allows to treat selectively respiratory tract by acquiring higher drug concentration in blood and simultaneously by decreasing the risk of occurrence of side effects due to the low level of applied drug in blood. Inhalants might be administered by means of different devices such as metered-dose inhalers also with spacers, dry powder inhalers and nebulisers.

Key words: asthma, chronic obstructive pulmonary disease, aerosolotherapy, inhaler, nebulisation.

Drugs administered via inhalation include drugs used in general anaesthesia, medicines applied locally in the respiratory tract (e.g. short-acting β2-adrenergic agonists, methylxanthines) and from some time general medicines. Drugs that are administered by inhalation are absorbed from the large surface of the alveoli and therefore they easily pass into the bloodstream. Medications for inhalation use must comply with several requirements (micronisation of molecules to sizes smaller than 5 μm, the corresponding quality of the aerosol generating device) increasing the costs of preparation of a form suitable for inhaled administration.

Respiratory diseases are the diseases affecting both children and adults. Treatment of respiratory diseases is long-lasting and complicated. Inhalation therapy is one of the most important methods of the treatment of respiratory diseases. The possibility of administering drugs directly into the bronchial tree often minimizes the serious effects of systemic medications, providing the desired therapeutic effect. Inhalation therapy allows for obtaining high concentration of medication in the site of pathological process with minimal risk of occurrence of systemic effects [1,2].

Asthma, one of the most common respiratory diseases is a chronic inflammatory condition of respiratory tract triggered by allergens, chronic viral or bacterial infections, occupational factors and intolerance of aspirin or other non-steroidal anti-inflammatory drugs. Image of the disease, its course and pathogenesis are heterogeneous. Inflammatory process, which takes place in the respiratory tract, causes breathlessness attacks, cough, wheezy breath and chest heaviness. Bronchial hyperresponsiveness is a hallmark of asthma. It is an excessive reaction of a respiratory tract to the stimulus, which is neutral for a healthy person (e.g. cough, exercise-

induced dyspnoea or dyspnoea induced by bronchial irritants – cold air, pollution). The most distinctive feature of asthma is the paroxysmal nature of symptoms that often occur at night or at dawn and are induced by exercise or environmental factors [3,4]. The following factors may cause asthma and frequent respiratory tract inflammations: allergens (house dust mites, moulds, animal hair, pollens, food), occupational factors (e.g. chemicals). Factors exacerbating the disease include: irritants (cigarette smoke, intense smells, smoke, air pollution), physical factors (laughing, crying, exertion, cold air), respiratory tract infections, emotional factors, medications (beta-blockers, non-steroidal anti-inflammatory drugs) and i.a. pregnancy and thyroid disease [4,5].

the formation of smooth muscle hyperresponsiveness. Structural cells, i.e. epithelium cells, smooth muscle cells, fibroblasts and inflammatory mediators produced by them, are also involved in the of bronchial damage [6, 7, 8].

Due to the factor eliciting bronchial spasms, asthma may also be classified as atopic bronchial asthma, caused by allergic reaction in the bronchial tubes and non-atopic asthma, in which allergic reaction is not observed [9]. In atopic asthma inflammatory process is triggered by the reaction of allergen with immunoglobulin E found in the receptors on basophile granulocytes and mast cells. These cells secrete numerous inflammatory mediators, which exhibit strong properties casing bronchial spasms,

Table 1: Classification of asthma severity

Level of asthma severity	Symptoms
Intermittent Asthma	• Symptoms occur less frequently than one time a week • Short-lasting exacerbations • Nighttime symptoms less than two times per month • FEV1>80% or PEF>80% of predicted of maximum value for a patient • FEV1 or PEF variability < 20%
Mild Persistent Asthma	• Symptoms occur more frequently than one time per week, but less frequently than one time a day • Exacerbations may disturb sleep and hinder daily activities • Nighttime symptoms more frequently than 2 times per month • FEV1>80%, PEF >80% • PEF variability 20-30%
Moderate Persistent Asthma	• Symptoms occur every day • Exacerbations may disturb sleep and hinder daily activities • Nighttime symptoms occur more frequently than 1 time per week • The necessity of every day inhalation of short-acting beta2 agonist FEV1 60-80% or PEF 60-80% • PEF and FEV1 variability >30%
Severe Persistent Asthma	• Symptoms occur every day • Frequent exacerbations • Frequent nighttime symptoms • Limitation of physical activity • FEV1 <60%, or PEF<60% • PEF and FEV1 variability >30%

In asthmatic patients bronchial obstruction occurs primarily as a result of structural changes in the respiratory tract. The inflammatory process in the course of this disease is characterized by an increased number of mast cells, which are responsible for eliciting bronchial spasms in response to an allergen or other stimuli (e.g. exercise, hyperventilation), and eosinophil cells, which together with other cells are involved in the later reaction, responsible for the chronic bronchial inflammation and

and pro-inflammatory cytokines, that also stimulate the migration of other cells (eosinophils and lymphocytes) to the site of inflammation [10].

In the diagnosis of asthma in addition to the basic physical examination and the chest X-ray, a very important test is spirometry. This test should be performed, even if the patient does not experience dyspnoea. To evaluate bronchial obturation, measurements of the maximum forced expiratory

volume after maximal inhalation (FVC – forced vital capacity) and the volume of air exhaled in the first second of the test (FEV1 – forced expiratory volume in one second) is necessary. Furthermore, the ratio of these two measurements (FEV1/FVC) should be calculated. Measurement of peak expiratory flow (PEF) is an additional test [4,10].

Another common condition of respiratory system is a chronic obstructive pulmonary disease (COPD) caused by inhalation of cigarette smoke. Cigarette smoke triggers a complex cascade of reactions leading to the damage to the bronchi and alveoli. It is characterized by incompletely reversible limitation of the airflow through respiratory tract. In the pathogenesis of COPD crucial importance has the activation of neutrophils and macrophages. Proteolytic enzymes, liberated from those cells, are the main cause of degradation of alveolar walls, what in turn leads to emphysema [9,12,13,14].

In the early stage, the course of COPD is often asymptomatic. The first symptom is usually a cough connected with expectoration and spitting the sputum out at first occurring in the morning. The diagnosis is determined by spirometry (reduction of forced expiratory volume in one second (FEV1) and increased forced vital capacity (FVC)). Typically, the disease progresses and even with the best treatment lung function deteriorates with time. In severe periods of the disease cough occurs throughout the day and also during the night. One of the late symptoms is dyspnoea, which occurs almost exclusively during physical exertion. As the disease progresses, complications emerge i.e. respiratory failure and cardiac failure. In the treatment of COPD particularly important elements include patient education, smoking cessation and rehabilitation programs [9,12,13,14].

Current classification used in the diagnostics of COPD is based on the results of spirometry. There are four stages of the disease: mild form, moderate form, advanced form and very advanced form [8, 14].

1. Drugs used in the treatment of chronic respiratory diseases

The aim of pharmacological treatment of asthma and chronic obstructive pulmonary disease is the reduction of bronchial hyperresponsiveness as a result of use of anti-inflammatory drugs and rapid removal of bronchial obstruction. Attempts are also made to prevent exacerbations and to prevent irreversible limitation of the airflow through the respiratory tract. Treatment is aimed at maintaining normal lung function and normal activity, including the ability to undertake physical activity. In addition, an important goal of the therapy is to avoid the side effects of drugs [5]. Treatment of asthma is a multispecialist treatment.

The principle treatment of asthma is pharmacological therapy, specific immunotherapy i.e. modification of immunological reaction (performed in some forms of atopic asthma), change of the environment, as well as patient education and psychotherapeutic effects [12]. Given the fact that mechanism of drugs effect used to treat asthma can be divided into two basic groups: drugs abolishing bronchial spasms and medicines preventing contractile responses induced by the action of early phase mediators and late phase of reaction to allergic inflammation. [5,12]

1.1. Drugs relaxing mooth bronchial muscles

Adrenomimetic drugs are the basic group of drugs used in every paroxysmal bronchospasm. Medications that stimulate beta-2 adrenergic receptors (located within smooth muscles from the trachea to the bronchioles, alveoli, epithelium cells, vascular endothelial tissue and on the mast cells) cause relaxation of bronchial smooth muscles (by decreasing smooth muscle tension). It clinically manifests itself with improved patency and improved spirometric indices. Moreover, they show direct effect on the allergic phase of inflammation, suppress the liberation of transmitter substances of allergic reactions. This action is also related to the prevention of bronchial spasms after inhalation of the substance that shrinks bronchi (histamine, methacholine) and the prevention of post-exertional bronchospasm.

Other activities of beta-2 adrenergic receptors are also important e.g. the improvement of mucociliary clearance and the improvement of diaphragm muscle function, decrease of pulmonary artery pressure and increasing the right ventricular ejection fraction [12]. Medicines that stimulate beta-2 adrenergic receptors differ in selectivity for β2 receptors and also in the beginning and duration of the effect. They also show varying degrees of severity of side effects. In the long-term treatment of spasmodic bronchitis currently only selective β2 – mimetic drugs are administered, showing no adverse effects when used at therapeutic doses. Adrenomimetic β2 drugs are divided into short-acting and long-acting, which are applied preventively [1,3,4,12,15,16].

Anticholinergic medicines are the second group of drugs loosening bronchial smooth muscle. These are the substances that nonselectively block the muscarinic receptor. Blocking of receptors of parasympathetic system causes bronchi relaxation, increasing density of mucosal cells' secretion, inhibition of secretion and production of the mucus, slowing the movement of cilia and mucus removal. The most

commonly used anticholinergics are ipratropium bromide in aerosol or nebuliser or tiotropium bromide in aerosol with long-lasting time of action. This group of medicines are indicated for use in long-term treatment of COPD as first–line drug as well as for the treatment of asthma as a second-line drug in case of exacerbation of the disease.[1,4,12]

Methylxanthines are used in the treatment of asthma, because they loosen the smooth muscles of bronchi, exhibit effects on the allergic inflammation phase, reduce bronchial hyperresponsiveness, reduce swelling of mucous membranes, and favourably affect the immune reactions occurring in the bronchi. In addition, they prevent the fatigue of the diaphragm and improve its contractility. The mechanism of methylxanthines effect is multidirectional: they block phosphodiesterases, increase the effect of β2 receptors, intensify the burst of Ca2 + from sarcoplasmic reticulum in the striated muscle. Methylxanthines are strong inhibitors of adenosine receptors – that block smooth muscle contraction, without affecting calcium penetration into the cell [4.16].

1.2. Drugs blocking allergic reaction and inhibiting allergic inflammation

Corticosteroids are an effective group of drugs controlling course of the disease. Favourable directions of corticosteroids effect in asthma treatment include reduced severity of symptoms, improved results of a function test, reduced frequency of exacerbations, number of hospitalizations and mortality in patients with asthma. Furthermore, glucocorticoids reduce bronchial hyperresponsiveness; the effect unfortunately disappears after cessation of their use. These drugs also inhibit the synthesis of cytokines, which are responsible for the ongoing inflammation in the respiratory tract of asthmatic people. Although corticosteroids inhibit inflammation, they do not cure the its cause [4,7,16,17].

Corticosteroids are strong anti-inflammatory drugs, acting at the genomic level. Anti-inflammatory action takes place on several levels and includes various types of cells and different mechanisms – glucocorticoids have an impact on differentiation and maturation of immunocompetent cells, apoptosis of inflammatory cells, and affect the genes responsible for the production of proinflammatory proteins. These drugs inhibit the activity of inflammatory cells, including eosinophils, lymphocytes, macrophages, mast cells and dendritic cells. Furthermore, they inhibit the inflammatory activity of epithelial and endothelial cells of pulmonary vessels and smooth muscles in the respiratory tract. [17]

The use of corticosteroids involves many therapeutic benefits i.a. the reduction not only of the clinical symptoms, but also decreasing the number of severe exacerbations, hospitalisation and emergency calls, improvement of lung function, reduction of inflammation in the respiratory tract, reducing the frequency of use of short-lasting β2-agonists and improvement of the life quality [7].

Corticosteroids are administered to patients with COPD. They reduce the severity of the symptoms, but they do not affect the natural course of the disease and constant decrease of FEV1. Corticosteroids administered orally and via inhalations do not affect the reduction of mortality of patients with COPD. Moreover, their impact on the ongoing inflammation of the respiratory tract was not revealed.

Table 2: The anti-inflammatory effect of corticosteroids in the respiratory tract [12]

Effects on cells
• reduction of the number of eosinophils and shortening their life span
• reduction of basophils and mast cells influx to mucous membrane
• reduction of the number of T lymphocytes in the epithelium of mucous membrane
• inhibiting the uptake and processing of antigen by Langerhans cells without affecting the antigen presentation
Effect on production and action of cytokines
• decrease of mRNA concentration and diminution of the level of interleukins and their receptors (IL-3, IL-4,IL-5)
• reducing the expression of adhesion molecules on the surface of mucosal epithelial cell
Other effects
• reduction of the release of mediators, preformed and synthesized de novo
• inhibiting vascular permeability and mucus production
• increasing the density of β2 receptors
• reduced extraneuronal uptake of catecholamines
• increased biosynthesis of kinin-decomposing endopeptidase and angiotensin-converting enzyme, participating in the inflammatory process

Ciclesonide is a new inhaled corticosteroid. It is a prodrug, which as the only inhalatory steroid can be administered in a single daily doses. Being the prodrug, it does not cause any side effects such as

oral cavity mycosis or hoarseness, because its effect is possible only after enzymatic activation by specific lung esterase. This process occurs also in the respiratory epithelium [18,19].

The use of corticosteroids involves numerous adverse actions, particularly in the general application. These include osteoporosis and muscular atrophy, irregular menstruation, hypothalamic-pituitary-adrenal axis suppression, obesity, change of body shape and appearance of the face, diabetes, hypertension, cataracts. Rarer complications include mental changes, ulcers, glaucoma [12.20].

Leukotriene antagonists are also used in the treatment of bronchial asthma. They inhibit the leukotrienes, which exhibit a very strong effect on smooth muscle and mucosa of the respiratory tract, cause the influx of neutrophils and eosinophils to the site of inflammation and contribute to the increased growth of bronchial smooth muscle cells, intensifying the process of remodeling i.e. reconstruction of the respiratory tract. Two categories of leuktriene antagonists can be distinguished. The first one is constituted by the antagonists of cysteinyl-leukotriene type 1 receptors CysLT1 (CysLT1 (montelukast, pranlukast and zafirlukast). To the second category belongs 5-lipoxygenase inhibitor (zileuton),which inhibits the synthetic pathway of leukotriene metabolism.

Leukotriene antagonists reduce the symptoms of bronchial asthma such as dyspnoea and cough, because they cause bronchodilation. Therefore, they improve lung function and inhibit the contraction induced by exposure to cold air and non-specific irritant compounds. Being safe and generally well tolerated, leukotriene antagonists cause relatively few side effects [12].

Chromones are anti-inflammatory drugs, which inhibit the early and late asthmatic reaction. Used together with inhalatory corticosteroids, they enable reduction of the applied dose of steroids. Being an inhibitor of the activity of respiratory tract sensory fibers, Nedocromil sodium has an antitussive effect. A very important advantage of chromones is almost complete lack of side effects. Chromones are recommended for episodic asthma and mild persistent asthma [1,10,16,17].

2. Aerosolotherapy

Aerosolotherapy is a field of science developing very rapidly, mainly due to technological progress. The word aerosol first used by Gray and Patterson in 1932 means a suspension of fine solid particles or liquid droplets in a gas. The range, distribution and location of the deposition of the drug depends on the size of particles generated during the production of aerosol. Air distance, distribution and the location of drug deposition depend

Table 3: Differences in the treatment of asthma and COPD [21].

Treatment	Asthma				COPD		
	Episodic	Mild persistent	Moderate persistent	Severe persistent	Mild form	Moderate form	Severe form
Short–acting beta2 agonists	++	+++	+++	+++	++	+++	+++
Long-acting beta2 agonists	-	+/-	+++	+++	-	++	++
Anticholinergics	-	-	+	+	+	++	++
Inhalation corticosteroids	+/-	++	+++	+++	-	+/-	+/-
Systemic corticosteroids	-	-	-	+	-	-	-
Leukotriene antagonist	-	+	++	++	-	-	-
Methylxanthines	-	+	+	+	-	+	+

on the size of particles generated during the production of aerosol. In the respiratory system particles of size ranging from 1 to 10 μm are retained. Particles larger than 10 μm subside mainly in the nasopharyngeal cavity and larynx, molecules sized from 5 to10 μm are deposited in the large bronchi, while molecules smaller than 5 μm are deposited in small bronchi and bronchioles, constituting the so-called low-molecular-weight fraction of aerosol [22, 23].

Drugs administered via inhalation either cannot be used in other forms or being administered in this manner have local effect and applied dosage of a drug may be relatively bigger. Drug administration in the form of inhalation helps avoiding systemic side effects [22,24].

Beta2 agonists, steroids and chromones used in asthma, chronic obstructive pulmonary disease or so-called spastic bronchitis are applied through inhalation. The use of inhalative drugs for the treatment of respiratory diseases has certain advantages over oral or parenteral administration, because it enables selective treatment of the respiratory tract by reaching high drug concentration, simultaneously minimizing systemic side effects due to the minimum drug concentration in the blood. Another advantage of inhlative drug is its painless nature and convenience [4,5,24]. Table 4 shows the indications for aerosolotherapy.

Table 4: The indications for aerosolotherapy

Indications for aerosolotherapy in respiratory tract diseases
• chronic rhinitis and laryngitis;
• chronic, non-specific inflammation of nose, pharynx and larynx with the presence of secretion;
• seasonal allergic rhinitis;
• recurrent and chronic sinus inflammation;
• chronic laryngitis: atrophic, hypertrophic and voice fatigue;
• mycoses of the oral cavity, pharynx and larynx;
• chronic and recurrent bronchitis;
• cystic fibrosis – pulmonary form;
• bronchial asthma;
• conditions after pneumonia, especially after chronic pneumonia or pneumonia with tendency to recurrence;
• respiratory fungal infections;
• conditions before and after surgical intervention in the area of respiratory tract

Inhalation medications may be administered with help of various devices i.a. pressurized metered-dose inhaler (pMDI), pMDI with spacer devices, dry powder inhaler (DPI) and devices for nebulisation. The purpose of aerosolotherapy is to hydrate secretion, dilate bronchi as well as to eliminate of inflammatory reactions [23,24,25].

2.1. Pressurized metered–dose inhalers (MDI)

In the metered-dose inhalers introduced in 1955, hydrofluoroalkane (HFA, non-CFC propellants, Freon-free) is a propellant. At the beginning of the last decade chlorofluorocarbon was commonly used (CFC formulations, so-called Freon ones). Releasing a dosage of medicine in such inhalers occurs as a result of rapid decompression of a carrier after pressing the valve. Unfortunately, only 5-10% of the drug reaches the bronchial tubes. The rest of a drug remain above (irritating effect on the upper respiratory tract and pharynx, systemic effect due to the possibility of swallowing). Proper technique of the inhalers usage that guarantees optimum effect requires synchronization of the start of inhalation with actuation of the device. This synchronization is particularly difficult for older people and impossible to be performed by children. It may be prevented by usage of add-on devices (spacers), which increase the effectiveness of administered drugs. Spacers keep the part of unnecessary medication on its surface [1,24,25].

There are 3 types of spacers:

- large spacers of 500-750 ml capacity, with or without a valve e.g. Volumatic – 750 ml chamber, intended for children older than 2.5-3 years; equipped with an inhalatory-exhaust valve and may be used without face mask; Aeroscopic – 750 ml chamber, intended for children above 3 years old.
- small spacers of 100-200 ml capacity, which are simple, valveless tube (open spacers); Optichamber – 210ml chamber, with a sound signal to ensure better control during drug administration; Able spacer – 125 ml chamber, fitted with a replaceable silicone masks in three sizes. It has sound signal that optimizes the way of medicine taking. It can be used in infants and young children. The flexible connector allows the use of MDI containers of various shape.
- little spacers with forced reverse flow – Dynahaler – enables the adoption of the drug in one long, deep breath, it is "unlocked" exactly when the drug portion of the pressure vessel is released [25,26].

2.2. Dry powder inhalers (DPI)

The dose is released from the DPI with air, which flows through the device during inhalation performed by the patient (so-called inhalation triggered dose). These inhalers require strong and short inspiration [24.25]. Dry powder inhalers differ in

a number of essential technical parameters and functional features. The main differences are: the method of aerosol generation and drug release, the internal resistance of the device, the optimal range of inspiratory flow, the presence of the carrier, the number of doses and a control system in the inhaler, as well as external physical features [24.27].

Aerolizer is the older form of dry powder inhaler. The capsule with a drug is placed in the device spinhaler type where its puncture occurs. After inhalation due to the deposition of particles of lactose in the mucosa of the mouth and throat, a patient has the sweetish taste sensation. Optimal conditions for inhalation with the powder dispenser of this type provide a high inspiratory flow (about 120 l / min).

Table 5: Table 5. Advantages and disadvantages of DPI. [28]

Advantages	Disadvantages
• administration of a drug is breath-activated • they require less coordination from the patient than the pMDI and enable easier usage • they do not require solvent and dditional substances • ensure high stability of the drug • small size • constant readiness to use • most DPI have a counter of doses • environment friendly	• they require a respectively strong inspiration to produce an aerosol • in most devices inspiratory flow rate determines the deposition of the drug • the necessity of measuring peak inspiratory flow in some patients • some devices provide a single dose • not all drugs are available in DPIs • higher production cost than pMIDs • use possible from the age of 4

Easyhaler is a a multidose, reservoir, highly-resistant DPI, which can contain 200 doses of the drug. It has a dose counter and a clear warning for the user before the last doses. A small number of actions needed to perform inhalation is also very important. Another advantage of Easyhaler is low optimal inspiratory flow – 28-60 l / min, which is required for the proper process of inhalation and high pulmonary deposition of the drug [27].

Disk is a newer type of powder inhaler (modified, advanced version of Diskhaler) with low internal resistance and a chamber with a drug placed near the mouthpiece. Single doses of the drug are placed on the spirally arranged foil tape in a plastic housing. The device has a dose counter. In contrast to Aerolizer, the optimal dose from the disk is obtained even at low inspiratory airflow (30 l / min).

Novolizer – the active substance is in powder form on lactose. The device is activated via the inhalation and during the inhalation the active substance is released from lactose particles on the principle of a rotational motion. The inhaler is characterized by low internal resistance. It has a dose counter and a system preventing accidental multiple dosing.

Turbuhalers operate as a result of turbulent air flow through the duct system. The drug is present in a pure form leaving no taste after inhalation. The device has a colour signalling system warning about the last 10 doses. In order to provide an optimal dose, it is necessary to inhale with inspiratory air flow rate of 60 l / min [26.28].

2.3. Nebulisation devices

Nebulisation is a method of aerosolotherapy, which consists of the delivery of a drug to the respiratory tract of a patient in the form of aerosol i.e. suspension of small liquid particles in a gas (dispersed phase). Compressed air (air nebulizers) or ultrasound waves are used to produce aerosol.

This method can be used in young children, the elderly, unconscious patients or patients with severe obstruction. Nebulisation is usually performed in patients in asthmatic condition in order to administer high dosages of medicines to loosen the bronchial tubes [22,23].

The advantages of nebulisation, that shall be listed include i.a. no need to coordinate inhalation and exhaust (possible use in children and the elderly), and thus, the cooperation with the patient, easy execution, the possibility of selecting an individual dose and the type of medication (beta2-agonists, antibiotics, proteolytic drugs or mucolytics) for each patient, the possibility of administering several drugs simultaneously. There is also the possibility of concomitant pharmacotherapy and oxygen therapy [23].

Nebuliser is a container for the drug solution in which the liquid form of the formulation is converted into an aerosol for inhalation. With respect to the volume of dispersed solution, there are two types of nebulizers: small volume nebulizers and large volume nebulizers, used mostly in hospitals.

Air nebulisers are built of a compressor generating compressed air or oxygen, nebulizer, drain and mouthpiece or mask. Compressed gas flows through a nozzle of nebuliser with the drug solution, generates an aerosol, whereas compressed gas is obtained by means of electric compressor or oxygen delivery

Table 6: Examples of nebulizers available in the market.

Sidestream	fitted with the Venturi system, which enhances the efficiency of air flow through a nozzle of a nebuliser during inspiration and simultaneously improves the production of aerosol (shortening of nebulisation time).
Personal Sidestream	a device intended for one patient, mainly in hospital
Ventstream	fitted with the set of filters to prevent penetration of aerosols into the ambient air (reducing the risk of transmission of pathogenic micro-organisms). It is particularly recommended for the nebulisation of antibiotics.
Pari LL	nebuliser with flow control system integrated with valve system, separating the inhale and exhale.
Pari LC Plus	intended for the patients in all age-groups

line. The quality of aerosol depends on the pressure of dispersed gas and the size of a nozzle. Increasing pressure enlarges the fraction of small particles. Drug deposition is dependent on the breathing volume, inspiration to exhalation ratio and inspiratory flow rate. The duration of nebulisation should not exceed 10 minutes, except for a constant nebulisation in the case of status asthmaticus.

Several types of air nebulizers can be distinguished: **classic nebulisers** with continuous aerosol production regardless of the breath phase; **breath-assisted nebulisers**, which work continuously, but owing to the system of valves, the production of aerosol is larger during inspiration; **with adaptation of the respiratory pattern** – nebuliser is controlled by the breaths and dosimetry, it works only during inspiration; **mesh nebulisers using** vibrations to produce nearly monodispersive aerosol of low velocity, which reaches the lower respiratory tract with high efficiency.

Among the nebulisers of intermittent production of aerosol the following can be listed: **nebulisers synchronised with the breath** (so-called dosimetric nebulisers), which produce aerosol only during inspiration, used i.a. in the inhalations of antibiotics; **adaptive aerosol delivery** (AAD), which monitor breathing rhythm of the patient and deliver the aerosol during the first phase of inspiration [22.23].

In the **ultrasonic wave nebulisers**, electronic oscillator generates a high frequency ultrasonic wave, which produce aerosol in contact with the surface of drug solution. The size of aerosol molecules depends on the frequency of waves and the properties of a solution i.e. mass density and surface tension. Usually particles from 1 to 5-8 μm are obtained. The advantage of the aerosol produced in ultrasonic wave nebulisers is its high density, which enables administration of higher doses of drug in a shorter time. Corticosteroids cannot be administered via ultrasonic wave nebulisers, due to the destructive effect on the structure of active particle [22,23].

3. Summary

Despite the large variety of inhalers available in the market, there are still many unsolved problems with asthma aerosolotherapy e.g. size and character of drug deposition in the lungs, systemic bioavailability of the drug, acceptation of this form of treatment by patients, selection of proper inhaler for a given patient and education of patients and their carers [28].

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