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Advances in inhalation therapy in pediatrics

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Abstract

Objectives: To review the most relevant articles regarding the technical aspects of inhalation therapy, inhalers currently available, and especially major advances in inhalation therapy in pediatrics.

Sources: Articles of MEDLINE database from 1983 were reviewed, in addition to book chapters, and the most important studies were selected according to the criteria established for this article.

Summary of the findings: Conventional nebulizers have a number of inconveniences, and breath-enhanced and breath-actuated inhalers are more attractive options. Among dry powder inhalers, we highlight those using passive and active powder dispersion mechanisms, which provide higher rates of drug deposition in the lung. Among pressurized metered-dose inhalers, we highlight breath-actuated, breath-coordinated, and velocity-modifying inhalers. These inhalers should be used preferably together with spacers, since the use of spacers produces a twofold increase in pulmonary drug deposition.

Conclusions: For children younger than 8 years, pressurized metered-dose inhalers with spacers are the most appropriate devices, since they provide a practical approach associated with greater lung deposition. In children older than 8 years who can generate high inspiratory flow rates, dry powder devices are best suited.

J Pediatr (Rio J). 2010;86(5):367-376: Nebulizers, pressurized metered-dose inhalers, dry powder inhalers, spacers, pulmonary drug deposition.

Introduction

Respiratory diseases are responsible for high morbidity and mortality among children, leading to a large number of emergency department visits by children in Brazil and worldwide. Among these diseases, we highlight the role of asthma, acute viral bronchiolitis, and diseases that present with recurrent wheezing in infants.[1-5]

Inhalation therapy is the cornerstone of treatment not only for patients with asthma, but also for wheezing infants both in acute episodes and in maintenance therapy when indicated. There are basically three types of inhalation devices: conventional nebulizers, dry powder inhalers, and pressurized metered-dose inhalers.[6,7]

The objective of this article was to review the most relevant publications regarding the technical aspects of inhalation therapy, focusing on the main advances in the various inhalation devices, their advantages and disadvantages, as well as to indicate which devices are best suited for each type of patient.

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Articles of MEDLINE database from 1983 were reviewed, and the most important and scientifically accurate studies were selected according to the criteria established for this review article. Relevant book chapters on the subject were also reviewed.

An aerosol is a suspension of a group of solid or liquid particles in a gas. The effectiveness of aerosol therapy depends directly on pulmonary drug deposition, which, in turn, is directly related to the size of the particles produced. Generally, those smaller than 5 μm are deposited in the distal airways, and those smaller than 0.5 μm tend to be exhaled during expiration.[8-12] However, in patients with chronic obstructive pulmonary disease, the ideal size ranges from 2 to 3 μm.[13-16] The size and density of aerosol particles are classified according to a mass median aerodynamic diameter (MMAD). For uniform-sized spherical particles, MMAD is defined as the particle diameter multiplied by the square root of the particle density. Another important factor is the particle size distribution or geometric standard deviation (GSD). By definition, GSD less than 1.22 indicates a monodisperse aerosol. Almost all aerosolized medications are heterodisperse, but the lower the GSD, the greater the proportion of particles close to MMAD.[1,3,5,6,17]

Mechanisms of lung deposition

The three basic mechanisms of drug deposition in the lung are: inertial impaction, gravitational sedimentation, and diffusion (Figure 1). Inertial impaction is the main mechanism for particles larger than 3 μm and is highly dependent on the inspiratory flow, and at high flow rates there is a greater trend toward deposition, even of smaller particles, in the upper airways. Lower flow rates, however, facilitate deposition in peripheral regions of the lungs.

Gravitational sedimentation reflects the effect of gravity on particles, which is not influenced by inertia, affecting primarily particles smaller than 2 μm, but also larger particles at low inspiratory flow rates. Breath holding for 5 to 10 seconds maximizes this mechanism, increasing the penetration of particles into the distal airways. Low tidal volume, relatively low vital and functional residual capacity, and shorter respiratory cycles in infants impair this mechanism.

Diffusion affects particles of such a small size that their movement is influenced mainly by Brownian motion, resulting in collision and coalescence of these particles against the airway structure and other particles.[6,18]

Conventional nebulizers

For years, conventional nebulizers were the only inhalation devices available.

Ultrasonic nebulizers (Figure 2) generate aerosol by rapid vibrations in a piezoelectric crystal. However, heat generated by the crystal can denature many drugs, particularly proteins, and the crystal may break, a fact that is often difficult to be detected.[19,20]

In jet nebulizers (Figure 3), aerosol is generated by Bernoulli's principle. Airflow or oxygen flow is forced through a tiny orifice and expands, causing a sudden fall in pressure and a great increase in velocity. By Bernoulli's effect, the solution within the nebulizer reservoir is sucked out generating aerosols. The larger particles are baffled out and drain back into the reservoir to be renebulized, and the smaller particles are inhaled. Compressed gas necessary for the operation of these devices may come from pressure cylinders or be obtained through the use of electric compressors.[21]

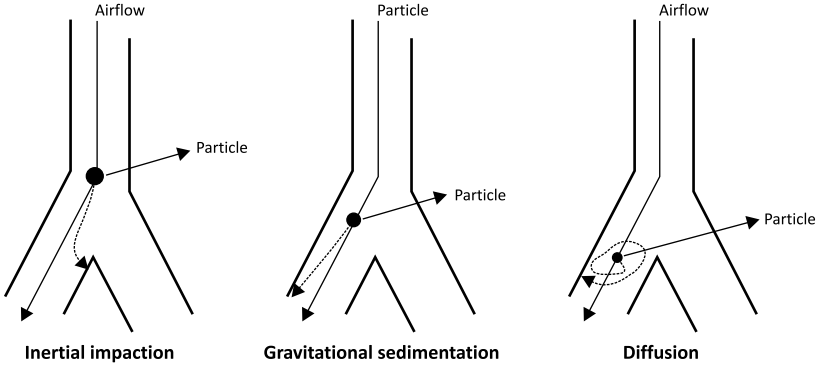

Figure 1 - Mechanisms of lung deposition

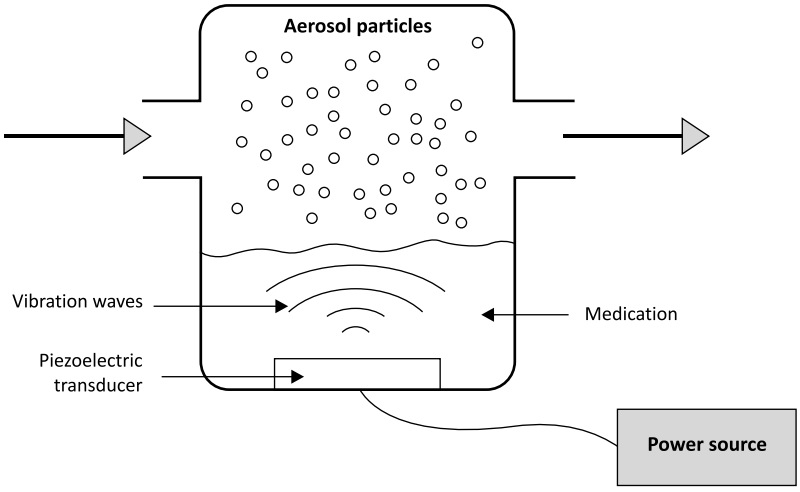

Figure 2 - Ultrasonic nebulizer

The effectiveness of nebulization is generally low, and there is considerable variability in device performance, which is influenced by nebulizer brand and, to a lesser extent, by fill volume, in addition to flow and humidity of the driving gas. As a result, it is difficult to predict the dose that is actually nebulized.[6,7,22-25]

In general, the above-mentioned inhalers are not very effective, achieving low rates of lung deposition, and are gradually losing ground to more modern and efficient devices.[20]

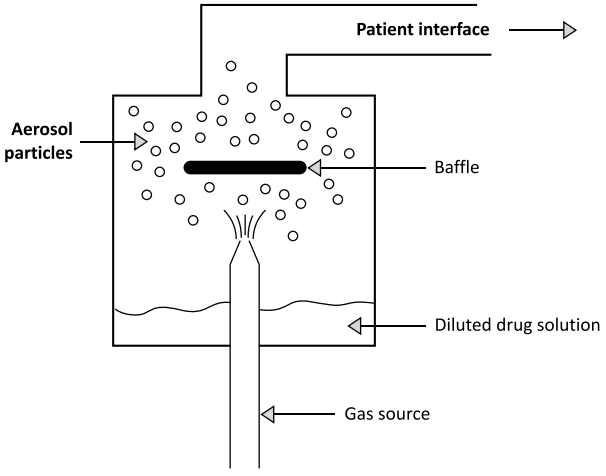

Figure 3 - Jet nebulizer

Novel nebulizers

Aiming to increase the degree of lung deposition of aerosolized drugs, nebulizers were improved, resulting in devices such as breath-enhanced nebulizers, optimized inhalation aerosols, and breath-actuated nebulizers.

Breath-enhanced nebulizers (Figure 4) have an inspiratory valve that allows the patient to inhale additional air during inhalation, in addition to recycling medication in the reservoir when the patient is not inhaling.[21] These are more efficient than old devices that do not have this recycling system (continuous nebulization), in which more than 70% of the drug is lost to the atmosphere during expiration. The only disadvantage of these devices is increased nebulization time.

Even more efficient and improved equipments may also be interesting alternatives. Among these, we can mention optimized inhalation aerosols that use the technology of vibrating mesh. Nebulizers that use this technology include the Omron NE-U22V MicroAir® nebulizer (Omron, USA), Aerogen's OnQ® aerosol generator (Nektar Therapeutics/ Novartis, USA), and Pari's eFlow TouchSpray® technologies (Pari, Germany), which use the vibrating mesh mechanism with an associated piezoelectric element (operating at frequencies lower than in ultrasonic nebulizers). This element vibrates at an aperture of a plate or mesh, acting as an electronic pump.

These nebulizers produce appropriately sized particles with high output rate (0.2 to 0.6 mL/minute) and residual volume less than 0.2 mL, since there is no recirculation of drug from baffles, minimizing evaporative loss and cooling of the drug. These devices are silent, portable, do not

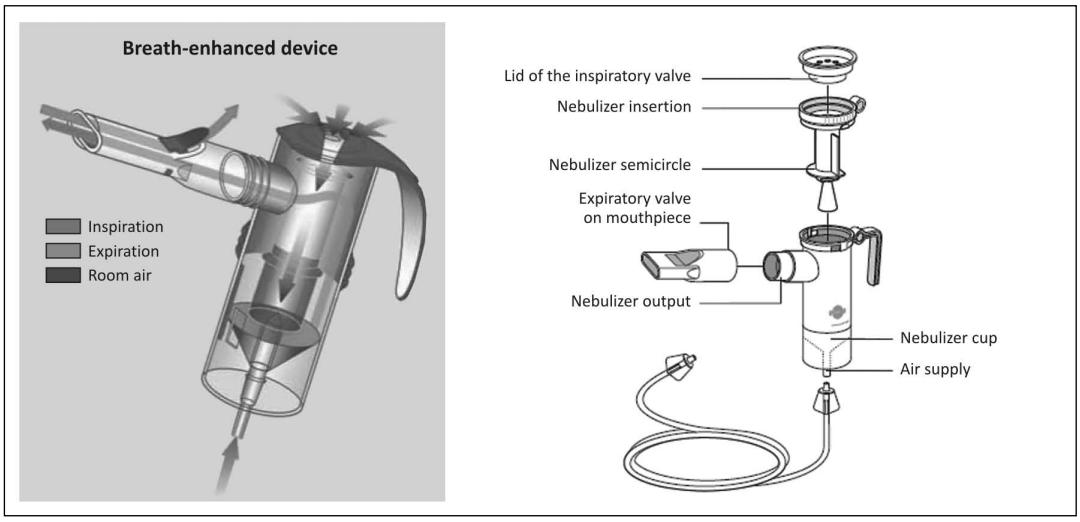

Figure 4 - Scheme of breath-enhanced nebulizer (Pari LC Star®, Pari Respiratory Equipment, Canada). Published with permission of the manufacturer

require compressed air, and can operate with batteries or alternating-current power, but are more expensive. Protein or gene drugs may be aerosolized with these devices, but some suspensions may clog the tiny holes of the mesh. The cleaning of holes and eventual replacement of the mesh are important aspects to maintain an efficient function. The performance of eFlow® may be adjusted for different formulations by controlling parameters such as hole size, number, and distribution, and power input to the piezoelectric element.

There are also breath-actuated nebulizers, such as AeroEclipse® (Trudell Medical International, Canada), which emit aerosol only when the patient inhales, reducing drug waste and contamination during inhalation. There are inhalers that, in addition to continually monitoring the patient's breathing pattern, adapt to changes based on a rolling average of the prior three breaths and release aerosol during the first 50-80% portions of inspiration. These equipments use adaptive aerosol delivery systems and, as an example, we can mention HaloLite® and Pro-Dose® (Respironics/Philips, USA). Similar to conventional nebulizers, the drawbacks for these inhalers also include that they are still compressor-driven systems, noisy, and need routine cleaning. The I-neb® (Respironics/Philips, USA), however, in addition to operating in a mode to deliver drug during the first portion of inspiration, operates in a mode that guides the patient to inhale slowly and aerosolizes drug during all but the last 2 seconds of inspiration to maximize lung deposition. Advantages associated with this device include that they are silent, portable, and provide minimal residual volume, optimizing the use of medications such as genes and high-cost drugs.[21,26-28]

Generally, the more modern devices mentioned above show satisfactory efficiency compared to conventional nebulizers, but at a much higher cost. However, it is worth remembering that there are some situations in which these devices are ideal, such as in inhalation therapy for cystic fibrosis patients.[21]

Dry powder inhalers

Dry powder inhalers are propellant-free devices in which a powder formulation of the drug is fractionated and micronized to produce respirable particles. In these devices, particle fraction is driven by the energy emitted from the user's inspiratory airflow. The drug powder may be used alone (as in Turbuhaler®, Astra AB, Sweden) or blended with lactose, as a carrier (as in Diskhaler®, GlaxoSmithKline, UK; Diskus®, GlaxoSmithKline, Research Triangle Park, USA; Rotahaler®, GlaxoSmithKline, UK; Spinhaler®, Fisons Corporation, USA; and EasyHaler®, Orion Farmos, Finland). These devices have several advantages: they are breath-actuated, simple, portable, and can contain multiple doses of the drug.[24]

The percentage of emitted dose that is deposited in the lungs varies among the different types of dry powder inhalers. These values may range from 15%, with the Diskus®, to 40% with the Spiros® (Dura Pharmaceuticals,

USA). However, a high inspiratory flow rate is required to actuate the dry powder inhaler (approximately 60 L/min), hindering its use in elderly and severely ill patients.[24]

A major concern in pediatrics is whether children can generate a satisfactory inspiratory flow while using these inhalers. De Boeck et al.,[29] in a study with 161 asthmatic children aged 5 to 17 years, assessed whether, after a 10-minute verbal training, these patients could correctly use the Turbuhaler®. One hundred thirty-three children (83%) performed every step correctly. Analyzing by age group, 96% of children older than 8 years performed every step correctly against only 55% of children between 5 and 8 years ($p < 0.001$). Of 28 children incorrectly using the device, 20 generated insufficient inspiratory flow.[29] Another disadvantage of dry powder inhalers includes particle agglomeration due to humidity, reducing the delivered dose.[24]

Novel dry powder inhalers

The large dependence on high inspiratory flow rates for the operation of the first dry powder inhalers led to the development of new technologies based on passive and active powder dispersion mechanisms. In both cases, the objective is to facilitate de-agglomeration of drug particles, resulting in greater lung deposition.

Devices using passive mechanisms include Novolizer® (Meda, Sweden) and Airmax® (Yamanouchi, Netherlands).[30,31]

The air classifier technology has been described as the most efficient passive powder dispersion mechanism currently used in dry powder inhalers.[32] In this case, multiple supply channels generate a tangential airflow that results in a cyclone within the device during inhalation. Novolizer® uses this technology and, when compared to Turbuhaler®, showed a greater degree of budesonide deposition in the lung and lower drug deposition rates in the oropharynx.[33]

A similar mechanism is used in the Airmax®. This inhaler has a separator within which the airflow generates a cyclone similar to that observed in the Novolizer®, and this device also has greater efficacy than Turbuhaler® with respect to total drug that is delivered to the lungs, according to studies with salbutamol and budesonide.[31]

The technology of dry powder inhalers has developed to use energy as a key element in the process of particle de-agglomeration. Storage of mechanical energy in systems based on springs or compressed-air chambers was one of the alternatives found in some devices. Exubera® (Nektar Therapeutics, USA), for example, uses an air chamber that is actuated by the patient through a kind of manual pump. The effectiveness of this device, which was designed for aerosolizing insulin, was tested and showed similar results with airflows ranging from 5 to 56 L/minute.[34]

Battery-powered, electrically driven systems have also become attractive options. Spiros® is a dry powder inhaler that operates appropriately even at very low inspiratory flow rates, exactly because it uses this principle to operate a twin-blade impeller that aerosolizes the drug.[35] In the treatment of critically ill patients, elderly or children younger than 8 years, this inhaler is an interesting option, since, in the case of beclomethasone, a study showed that an inspiratory flow rate of 15 L/minute generated lung deposition of 40.5%, greater than that achieved with flow rates of 30 L/minute (37.5%) and 60 L/minute (30.4%).[36] Another battery-operated device that is highly effective at inspiratory flow rates as low as 15 L/minute is the MicroDose® (MicroDose Technologies, USA), which uses a vibrating piezoelectric element to generate an aerosol cloud for the patient.[37]

In relation to passive powder dispersion mechanisms, active mechanisms have the advantage of showing lower rates of variability among doses delivered to different patients.[38]

Advancements in these inhalers also include new types of powdered formulations of drugs through the production of microparticles by spray-drying techniques, resulting in porous particles, with low geometric diameter and high potential for lung deposition. Similar porous particles may be coupled to long-sized carrier molecules to reach the lungs with similar efficacy.[38] Drug encapsulated liposomes are also a prospect of further improvement of drugs used in these devices.[39]

Delivery of inhaled insulin via powder devices is one of the advances that may provide a considerable gain in quality of life for a large number of patients.[38]

In Brazil, the following dry powder inhalers are available: Turbuhaler®, Aerolizer®, Diskus®, Pulvinal®, and Handihaler®.[40]

Pressurized metered-dose inhalers

Pressurized metered-dose inhalers (Figure 5) are the inhalation devices most commonly used worldwide. Their introduction has optimized drug supply, mainly bronchodilators and corticosteroids, to the lungs of adults, children and infants, in addition to reducing local and systemic side effects.[6,7,16,41,42]

Figure 5 - Pressurized metered-dose inhalers

The pressurized metered-dose inhaler is a safe and portable device, with multiple doses, which does not require a power source to be operated.[16,43,44] This device consists of a reservoir coupled to a plastic part, which contains the drug solution or suspension with surfactants, lubricants, and propellants, at a pressure of approximately 3 atm, depending on the type used. Traditional metered-dose inhalers are able to generate a percentage of lung deposition ranging from 10 to 20%.[45]

Types of propellants

Traditionally, chlorofluorocarbons (CFC) were used as propellants in metered-dose inhalers, but due to the recognized impact of these gases upon the ozone layer, hydrofluoroalkanes (HFA) are gradually replacing CFCs in this function.[28,46]

Ibiapina et al. published an extensive review regarding the use of HFAs as propellants for these devices. Formulations using beclomethasone with HFA, compared to those containing CFC, produce low-velocity aerosols, with smaller particles that provide greater lung deposition. This increase in lung deposition was also observed with other drugs, such as fluticasone and flunisolide. Initial data also indicate that HFA may be an economically advantageous option.[47]

Advances in pressurized metered-dose inhalers

Undoubtedly, pressurized metered-dose inhalers have been a success in terms of efficacy and patient acceptance. However, some aspects of these devices needed improvement.

The first advances were related to the valves used in conventional metered-dose inhalers, which enabled reduced dependence on the force applied to the reservoir in the reproducibility of the doses delivered, as well as the maintenance of this reproducibility with the progressive use of the device.[48,49]

An apparently simple, but important, aspect concerns the patient's perception of when the canisters are empty. To overcome this problem, dose counters were developed, which may be direct (based on an active firing mechanism, actuated by temperature or pressure changes) or indirect (based on a digital pressure or movement on the reservoir).

Direct mechanisms are more reliable, since they are directly related to dose release, but with a more complex manufacturing process. Indirect mechanisms are simpler and all dose counters currently marketed are of this type.[50,51]

However, more significant advances, related to the direct operation of metered-dose inhalers, were required not only to improve patients' comfort, but also to increase the effectiveness of the devices. Based on this objective, breath-actuated pressurized inhalers, breath-coordinated metered-dose inhalers, and velocity-modifying inhalers were developed.

The great advance of breath-actuated inhalers lies in overcoming the difficulty of many patients to coordinate firing the dose with initiating inhalation. In the late 1970s, the Autohaler® (Ivax Corporation, currently Teva, USA) was introduced, which initially required high inspiratory flow rates for good performance, besides being very noisy.[52] This device was redesigned, and a scintigraphic study showed that patients with low level of coordination and negligible levels of lung deposition of salbutamol with a conventional metered-dose inhaler achieved up to 20% of drug dose deposition using Autohaler®.[53]

MD Turbo® (developed by Respirics, USA) and K-Haler® (Clinical Designs Ltd, UK) are also based on mechanical devices that increase the effectiveness of inhalers. In the first, the movement of a small propeller generated by airflow releases a spring that presses the reservoir.[54] The second uses the K valve®, which is an evolution of that used in conventional metered-dose inhalers.[54]

Most breath-actuated metered-dose inhalers are unsuitable for children younger than 5 years,[55] but Easi-Breathe® (Ivax Corporation, currently Teva, USA), besides being simple to use, can be coupled, if necessary, to medium- and large-volume spacers, facilitating treatment in this age group.[54]

SmartMist® (Figure 6), produced by Aradigm Corporation, USA, has a microprocessor that records the patient's inhalation pattern and only actuates the device when a predefined combination of inspired volume and flow rate is achieved.[56]

Figure 6 - SmartMist® (Aradigm Corporation, USA). Published with permission of the manufacturer

An English study, which analyzed a large database of primary health care for one year, assessed 5,556 asthmatic children and adults of whom 306 used breath-actuated metered-dose inhalers and 5,250 used a traditional metered-dose inhaler. Patients in the first group required significantly less β2-agonists, oral steroids, antibiotics, and healthcare resource use than patients in the second group.[57]

Two other new categories of pressurized metered-dose inhalers include breath-coordinated and velocity-modifying inhalers. The great advantage of the first is to assist patients to achieve the necessary inspiratory coordination. These devices operate by opening small inhalation channels when the patient manually actuates the inhaler, reducing the resistance to inspiratory flow. An example is the Optihaler® (Respironics, USA).[58]

Velocity-modifying metered-dose inhalers reduce aerosol velocity when it is released from the device, reducing drug deposition in the oropharynx. The Spacehaler® (Evans Medical, UK), for example, is compact and has an actuator orifice capable of producing a swirl of particles in the aerosol, reducing its velocity.[59] A scintigraphic study showed that this device can achieve lung deposition rates similar to those of conventional metered-dose inhalers, with reduced deposition in the oropharynx, since much of the drug is usually retained in the actuator.[60] Tempo® (Map Pharmaceuticals, USA), in addition to generating a swirl of particles capable of reducing aerosol velocity, is breath-actuated and can be fired at different stages of the inspiratory cycle, so that different drugs and formulations can be directed to different lung zones.[61]

It is worth noting that, due to the progressive increase of inhalers using HFA as a propellant, which typically produce slower aerosol sprays, the impact of technological innovation of velocity-modifying devices has been reduced.[54]

Soft mist devices

A device known as "soft mist" is thus named because it uses a spring-like mechanism to drive the liquid through its end, generating an aerosol cloud for 1 to 1.5 seconds. An example is the Respimat® (Figure 7), manufactured by Boehringer Ingelheim, Germany, which is portable, propellant-free, easy to use, and can carry several doses; in addition, spacers, batteries or any power source are not required for its operation. In adults, lung deposition with this device is around 40%.

Other inhalers contain electronic components that assist the patient in the adjustment to the inhalation technique, the release of drug dose in the ideal moments of inspiration, in addition to storing information about the use of the device, which can be accessed by the physician, optimizing the supervision of patient adherence to treatment. AERx® (Aradigm Corporation, USA) is a device that has these characteristics.[27]

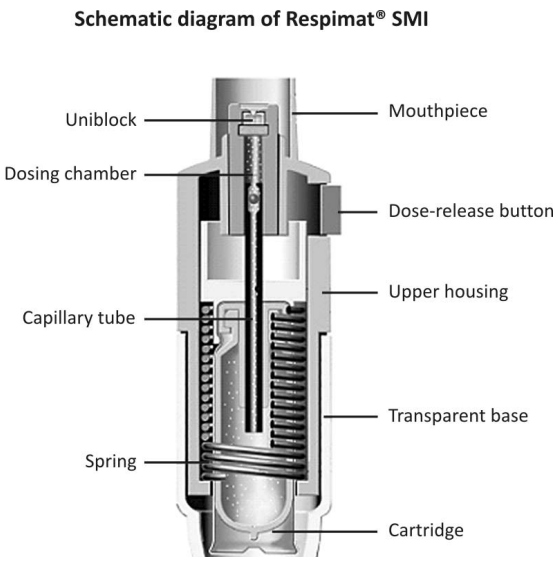

Figure 7 - Schematic diagram of Respimat® (Boehringer Ingelheim, Germany). Published with permission of the manufacturer

Spacers

It is recommended that metered-dose inhalers are used together with spacers (Figures 8 and 9), since spacers minimize the difficulty of many patients to coordinate firing the dose with initiating inhalation. Moreover, their use produces a twofold increase in pulmonary drug deposition, reducing impaction in the oropharynx and side effects associated with inhaled corticosteroid therapy, such as irritation in the oropharynx, dysphonia, and candidiasis. There are several types of spacers available in the market, varying in volume (113 to 750 mL), shape (cylinder, cone, pear-shaped, sphere), valve system, and material (plastic, metal). There are also homemade spacers, made from smooth plastic bottles, which have shown satisfactory efficiency. Some patients, however, do not like using spacers due to their size and need for cleaning and maintenance.[6,24,43,44,62,63]

Figure 8 - Plastic spacers with face mask and mouthpiece

Figure 9 - Metal spacer and face masks. Vortex® (Pari Respiratory Equipment, Canada). Published with permission of the manufacturer

Modern, valved spacers made of metal, a non-electrostatic material, are the best option for combined use with metered-dose inhalers.[64] In children younger than 4 years, spacers should be used connected to a face mask, and in older children, a mouthpiece should be used.

Conclusions

Inhalation therapy is the mainstay of treatment of patients with asthma and also of wheezing infants in certain situations, for example, when there are signs suggestive of early-onset asthma, such as history of asthma or parental atopy, atopic eczema, wheezing out of viral infections, eosinophilia, among others.[1]

For children younger than 8 years, pressurized metered-dose inhalers should be the device of choice, since they provide a practical approach associated with greater lung deposition when used together with spacers. Their use should be encouraged not only in maintenance therapy with inhaled corticosteroids, but also in the treatment of acute exacerbations during emergency medical visits, since it is known that the combined use of metered-dose inhalers with spacers in the treatment of acute asthma is more efficient and shows less side effects and greater convenience when compared to the use of conventional nebulizers.[25,41]

With respect to costs, a study conducted in a private tertiary hospital in Los Angeles, USA, with patients admitted for obstructive pulmonary diseases, concluded that self-administration of bronchodilators with pressurized metered-dose inhalers and spacers, compared to conventional nebulizers, could generate savings of US$ 253,487 per year.[65]

In Brazil, Vilarinho et al.[66] compared the use of salbutamol via metered-dose inhalers with homemade spacers (made from empty bottles of saline) with conventional nebulizers in the treatment of 54 children with acute asthmatic crisis. Both devices showed similar efficacy, but the total treatment cost for the group using metered-dose inhalers accounted for 22% of the costs concerning the patients who used conventional nebulizers ($p = 0.0001$). It is noteworthy that this study did not consider total expenditure with oxygen use in the latter group. Time spent with the use of homemade devices was also significantly lower.[66]

Also in Brazil, Chong Neto et al.[67] evaluated the use of salbutamol in the treatment of 40 children with mild to moderate acute asthma by four methods: conventional nebulizers, metered-dose inhalers with industrial spacers, metered-dose inhalers with homemade spacers, and dry powder inhalers. There was no clinical difference between the four treatments, but the use of metered-dose inhalers with homemade spacers was the most economical option, followed respectively by powder devices, metered-dose inhalers with industrial spacers, and nebulizers. This study reaffirms that the use of metered-dose inhalers with spacers in a hospital environment is economically advantageous when compared to the use of nebulizers.[67]

When addressing the issue of the economic impact of asthma, one must remember that the direct costs to treat this disease correspond to the amount spent on medication, devices, medical visits, and hospitalizations.[68] When optimized, however, treatment of this disease may reduce not only its direct costs to society, but also the indirect costs, which involve school and work absence, loss of productivity, early retirement, and death.[68]

Taking into account that Brazil is a developing country, with an overburdened public health system and a significant portion of the population living under precarious socioeconomic conditions, any savings generated through the management of a disease as prevalent as asthma is essential both for the population and for the health system.

However, in order to achieve the maximum benefits from the use of metered-dose inhalers, it is vital that the inhalation technique be accurate. There is evidence that not only patients, but also health professionals have serious deficiencies on how to correctly use these devices.[69]

Finally, it is worth mentioning that in children older than 8 years dry powder devices are best suited for maintenance therapy, remembering that, for crisis management, metered-dose inhalers should be used, since there are no short-acting bronchodilators in the form of dry powder inhalers currently available in the Brazilian market.

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