INHALATION THERAPY IN ASTHMATIC AND NOT ASTHMATIC CHILDREN

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The use of inhaled aerosols allows selective treatment of the lungs directly by achieving high drug concentrations in the airway while reducing systemic adverse effects by minimizing systemic drug levels. Aerosol drug delivery is painless and often convenient, but the proliferation of inhaler devices has resulted in a confusing number of choices for clinicians who are selecting a delivery device for aerosol therapy. There are advantages and disadvantages associated with each device category. Several factors can guide clinicians to choose a device for a specific patient. This choice has to be tailored according to the patient's needs, situation and preference. Whatever the chosen inhaler, inhaler technique is the critical factor in the correct use of delivery devices and patient education has a key-role for improving technique and compliance.

The use of inhaled aerosol allows a direct and selective pharmacological action useful in many respiratory diseases, such as asthma is one of the most common chronic diseases worldwide with a prevalence increasing in many countries, especially in children.[1-5]

Physicians currently have a choice of 3 types of dispensers for lung deposition of drugs: nebulizers, pressurized inhalers (MDIs) and dry powder inhalers (DPIs). [6]

NEBULIZERS

Nebulizers can be used by adults and children also in acute situations. Nebulization continues to be used in hospitals because requires little teaching for use and poor cooperation by the patient. They can be loaded with higher drug dosages and contain no propellant.[6,7,8] To avoid the medication wastage of the first devices, newer and more efficient nebulizers have been developed. Breath-enhanced nebulizers had the shortest treatment time with greater pulmonary deposition, while breath-actuated nebulizers reduced drug waste (figure 1).[6,9-12]

INNOVATIONS: Recently, "mesh nebulizers" use a microperforated vibrating mesh that has multiple apertures to produce the aerosol.

A piezoelectric crystal vibrates at high frequency when electrical current is applied, and the vibration is transmitted to a transducer horn that is in contact with the solution. Vibration of the transducer horn causes upward and downward movement of the mesh plate. So the liquid passes through the apertures in the plate and form an aerosol. The aerosol particle size and flow are determined by the exit diameter of the aperture holes (Figure 2).[10]

Drug delivery with the vibrating-mesh nebulizer was 2-4 fold greater than with the jet nebulizer in pediatric and adult models.[13] This technology offers a close control of the droplet size that is being generated and targeted to reach the lower airways, with little oropharyngeal deposition, thereby reducing undesired side effects. The greatly improved efficiency of such devices provides further advantages for the patient. Portability, shorter drug-delivery time and noiseless operation have a positive effect on patient compliance. The main disadvantages are the expensive price and the dependence on fluid characteristics, because these nebulizers may be unsuitable for viscous fluids. [10,14]

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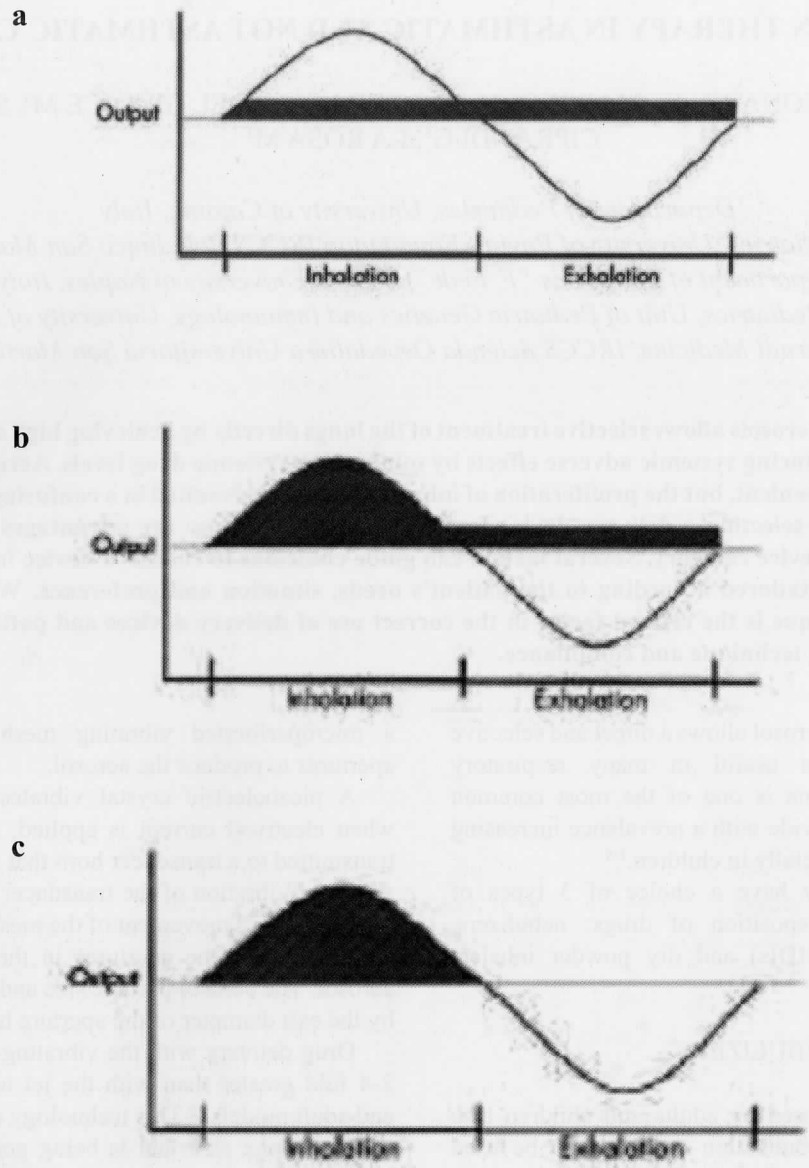

Fig. 1. *Nebulizer output. a. Jet nebulizer; b. Breath-enhanced nebulizer; c. Breath-actuated nebulizer. In each figure, the aerosol output of the device is indicated by the shaded area.*[11]

The Table 1 put to comparison some of the nebulizers currently used in Italy.A LOOK TOWARD THE FUTURE: I-neb AAD System

The latest generation of "intelligent" nebulizers is based on a vibrating mesh nebulizer platform coupled with Adaptive Aerosol Delivery (AAD) technology. The I-neb AAD System has a minimal residual volume and it has been designed to continuously adapt to changes in the patient's breathing pattern, and to pulse aerosol only during the inspiratory part of the breathing cycle. This eliminates waste of aerosol during exhalation and creates a foundation for precise aerosol dose delivery. With the introduction of the hydrofluoroalkane propelled pressurized metered-dose inhalers and as previously noted with some DPIs, patients are often unsure about whether they have actually received a dose from their inhalation device. To overcome this difficulty, the I-neb AAD System provides a feedback to the patient in the form of a smiling face on the LCD screen, a buzzer and vibratory signals when nebulization of the dose preprogrammed on the AAD Disc is completed. It is a portable system that contains a rechargeable battery, provides noise-free

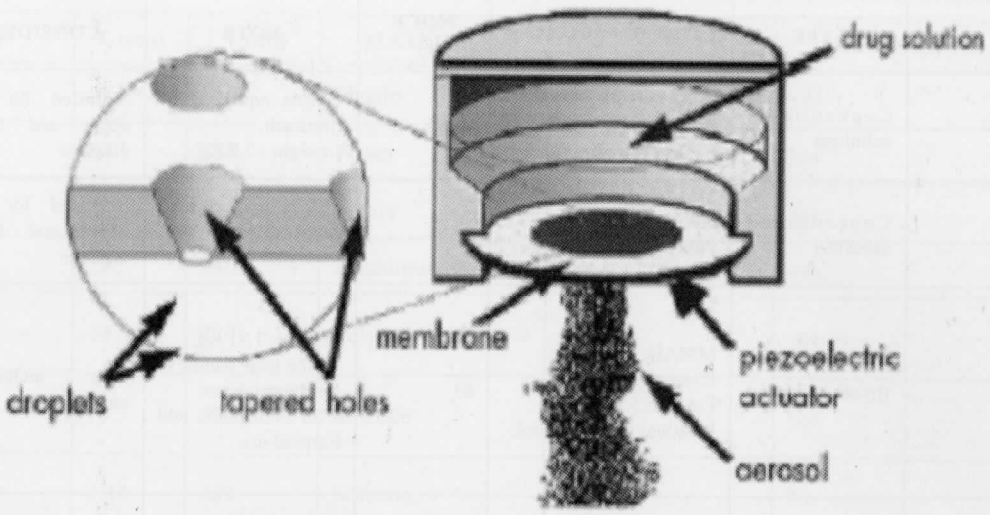

Fig. 2. *Principle of operation "mesh nebulizers".*[11]

operation and there is a potential for a single platform to deliver multiple inhaled drug therapies. The most attractive feature is a memory chip and an infrared interface to transmit the data to a computer; it allows monitoring of patient adherence. Data from the AAD Disc can be downloaded via a modem to a monitoring station. These data are reviewed and an electronic prescription request (generated for a pharmacy) makes arrangements to deliver the treatment to the patient's home The I-neb AAD System is suitable for delivering several drugs and α1 antitrypsin. In addition to potential benefits, such as improved aerosol delivery and drug deposition, shorter drug-delivery time may serve to improve adherence to treatment regimens.[15-19]

DRY POWDER INHALERS (DPIs)

Dry powder inhalers are efficient, pocket sized and do not require any proper maintenance or external source of energy to deliver the aerosol. Most DPIs have a dose counter for multi-dose medications. It is relatively easy to teach proper technique for using these devices and many old children and adults prefer DPIs to either pMDIs or jet nebulizers. The main advantages are that DPIs are activated when the patient inhales and do not require any hand-breath coordination. [4,6,7,20]

Because dry powders tend to aggregate, medication given by DPI needs to be de-aggregate to form an appropriate particle size for inhalation. Some DPIs require an inspiratory flow > 60 L/min to effectively de-aggregate the powder and that flow cannot always be achieved by children and patients with severe airflow obstruction.[20-30] All DPIs are humidity sensitive. If patients exhale into the device, they risk blowing out the medication and the humidification from exhaled breath can decrease the efficiency of the inhaler as the particles stick to the orifice. [3,7,20,31-33]

PRESSURIZED METERED DOSE INHALERS (pMDIs)

The pMDI has the practical benefits of small size, portability, unobtrusiveness and relatively low cost. pMDIs have multi-dose capability and a dose can be delivered quickly. Another advantage is the high reproducibility between doses.[7,34,35]

The disavantages are:

- the lack of a dose counter;
- the high deposition in oropharynx (immediate gargling and rinsing after inhalation is useful for removal of drugs following inhalation of drugs);
- the high dependence on patient technique; misuse can

Table 1: Nebulizers currently used in Italy.

TRADE	TYPE	CHARACTERISTICS	PRICE (€)*	NOTE	CONSIDERATIONS
Bimboneb	Conventional nebulizer	MMAD: 1,85 µm; Pmax: 2,5 bar; F max: 12L/min	80,65	- it is equipped of rinowash; - weight : 2,9 Kg	Indicated for treating the upper and lower airway diseases
Nebula	Conventional nebulizer	MMAD: 1,9 µm; output: 0,3 ml/min; Pmax: 3 bar; Fmax: 12 L/miin	79,98	- it is equipped of rinowash; - weight : 3 Kg	Indicated for treating the upper and lower airway diseases
Medel Pro	Breath enhanced	MMAD: 1,8 µm; Pmax: 2,5 bar; Fmax: 5,5 L/min; Residual volume:0,5ml;	63	-weight: 1,91 Kg ; - retractable handle - for intensive use - for both home and hospital use	New technology and contained cost
Medel Family	Conventional nebulizer	MMAD: < 5 µm; Pmax: 2,3 bar;	45	- only for home use; -ultra compact (1,55 Kg)	The most important advantage is the price
Clenny³ Aerosol	Breath enhanced	MMAD: 2,1 µm; output: 0,3 ml/min; min;	89	- small and portable (315-550g); -not for intensive use;	
Clenny² Aerosol	Breath enhanced	MMAD (50%): <5 µm;	49	-portable (300g)	Advantages: Small and new technology.
Aerosol e-Flow Rapid	ultrasound with mesh technology	MMAD: 4,1 µm;	1.400	- silent; - time of treatment reduced of 50%; -portable (300g);	it is currently the most innovative available device, but it is expensive
Aeroneb-aeroneb go	ultrasound with mesh technology	MMAD: 1-5 µm;	189	-silent; -easy; -portable (60-260 g);	it is currently the most innovative available device and it's not expensive
Alphaneb AE02	Conventional nebulizer	MMAD: 4 µm; P max: 1,5 bar;	35		

*MMAD=Mass Median Aerodynamic Diameter; Pmax= pressure max; Fmax= Flow max; *the price is indicative*

result in a suboptimal (even zero) lung deposition.[4,34,36]

Spacers used with MDIs compensate the problem of poor technique and decrease the incidence of any localized adverse effects in the mouth caused by oropharyngeal impaction of the drug during inhalation. Spacers also improve lung deposition. [35] The Table 2 show the features of the principal spacers. INNOVATIONS: The new MDIs (such as the Qvar, ciclesonide and Fostair) emit ultrafine particles. They not only improve lung deposition with good penetration throughout all the airways, but provide similar lung deposition when inhaled with a poor technique. When using these devices, oropharyngeal impaction is much lower and coordination is not important; in one study, lung deposition following actuation before and after the start of the inhalation was 37% and 50%, respectively, compared to 60% with good coordination. Because lung deposition from other MDIs is usually less than 15%, inhalation technique and oropharyngeal coordination are not as important for devices emitting ultrafine particles as they are for other

Table 2. *Principal Italian Spacers.*

NAME	L (cm)	V (ml)	MATERIALS	ANTISTATIC	MASCHERA	PRICE (€)*
Babyhaler	32	350	Plastic	No	yes	27(32)
Volumatic	23	750	Plastic	No	No	15,49
Fluspacer	20	305	Terlux	Yes	yes	17,50
Vortex	15	210	Aluminium	Yes	yes	24,50
Espace	14	220	Polycarbonate	No	yes	25/30
Funhaler	19,5	225	Silicone	No	yes	49
Watchhaler	21,8	300	Silicone	No	No	29,90
Aerochamber	11	145	Polymer Z-Stat	No	yes	25,60 39,50 40,50

*L= length; V= Volume; *price is indicatve.*

MDIs. This is an important advantage. [37-41]

RESPIMAT: SOFT MIST INHALER

Respimat Soft Mist Inhaler functions by forcing a metered dose of drug solution through a unique and precisely engineered nozzle (the uniblock), producing two fine jets of liquid that converge at a pre-set angle. The collision of these two jets generate the soft mist. Generation of the soft mist is purely mechanical, so propellants are not necessary. The Respimat, compared to a pMDI with fenoterol plus ipratropium bromide, provides equivalent bronchodilation at half the cumulative dose, compared to a conventional pMDI in asthmatic patients. Scintigraphy studies have shown that, compared to a pMDI, lung deposition is doubled and oro-pharyngeal deposition is reduced. [10,42-44]

CHOOSING AN INHALATION DRUG DELIVERY SYSTEM

Not all asthma inhalers are the same and choosing the most appropriate inhaler device is as important as choosing the right medication because can maximize asthma management and optimize overall clinical outcomes. [37,45]

Several factors can guide clinicians to choose a device for a specific patient. This choice has to be tailored according to the patient's needs, situation and preference.

One factor is the age of the subject. The SIP (Italian Society of Pediatrics) guidelines (based on GINA guidelines) for asthma management stress that specific inhaler devices should be used in different age groups of children. Children, aged 4-6, should be treated by pMDI + spacer , while in children aged 6-12 there is no significant difference between pMDI and DPI.[5,46] Also the British Guideline on the Management of Asthma stress this concept. [47]

The most important factor is that the efficacy of inhaler therapy often depends on whether it is carried out correctly. [2,6] Some recent meta-analyses show that the clinical results for a given drug offered by different dispensers are substantially equivalent if used correctly, but poor compliance and errors of inhalation technique are common in real life. For this reason, the physicians and all medical staff who see patients using aerosol therapy should teach the "correct use" of the dispensers and regularly check that this has been learned and continues to be put into practice. [2,6,41] The most important considerations are compliance, device and technique. Subsequently, healthcare professionals should prescribe the least costly product that is suitable for the patient.

Finally, choosing a device preferred by patients (due to its ease of use) can help optimize actual disease control. [37] The availability of pre-constituted combinations of drugs in one dispenser can increase the clinical efficacy of the treatment, as well as encourage compliance and using the same type of device for all inhaled drugs may facilitate patient teaching and decrease the change for confusion among devices that require different inhalation techniques. [6,48]

The objective of an ideal and easy-to-use inhaler is far from reality. Patient education is the critical factor in the correct use of delivery devices and a common effort is required in term of education among physicians, users, manufacturers of drugs and aerosol dispensers, in order to achieve the best results. [6] 39-67% of nurses, doctors, and respiratory therapists are unable to adequately describe or perform critical steps for using inhalers.

As clinicians we must understand how to use and differentially select and match the best device for the individual patient. We must adapt modern teaching techniques to optimize the effectiveness of our teaching efforts. As patient-care advocates we need to educate administrators and legislators of the need to make time for teaching and provide resources so that proper education is the norm rather than the exception.[49]

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