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Compressor/nebulizers differences in the nebulization of corticosteroids. The CODE study (Corticosteroids and Devices Efficiency)

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Abstract. – *Background:* **Nebulization is a common method of medical aerosol generation and it is largely used by adults and children all over the world, both for emergency treatment of acute illness and for long-term home treatment of lung diseases. The aim of this study was to determine the differences in nebulization of inhaled corticosteroids among four representative types of compressor/nebulizers.**

Methods: **Twelve compressor/jet nebulizers from four commercial sources were studied (three for each type): Clenny (MEDEL), Turbo Boy/LC Plus (PARI), Nebula Nuovo/MB5 (MARKOS MEFAR) and Maxaer (ARTSANA) compressor/Sidestream (Medic-Aid Ltd.) nebulizer.**

We compared the required time for the treatment (nebulization time), output/minutes, compressor pressures, and aerosol characteristics of inhaled corticosteroids: Beclomethasone dipropionate, Flunisolide, Fluticasone propionate and Budesonide.

Results: **Nebulization Times showed a significant difference between nebulizer and inhaled corticosteroids for Clenny, Turbo Boy, and Maxaer. A considerable difference in the output of nebulized drugs was observed through the compressors/nebulizers. MMAD of all inhaled corticosteroids was significantly different among the four nebulizers.**

The percentage of particles < 5 µm (respirable range) was high for all devices with beclomethasone and budesonide (> 90%), whereas with flunisolide was good only for Clenny (98.8%) and Maxaer (96.3%), and with fluticasone only for Clenny (98%), Turbo Boy (99.1%), and Maxaer (86%). Also percentage of particles < 2 µm showed significant variability among the devices.

Conclusions: **Our results clearly demonstrate that compressor/nebulizer unit plays a key role in the effectiveness of the treatment during inhaled corticosteroid therapy, and that several differences exist in the performance of the different nebulizers studied. Therefore, the device has the same importance of the compound to reach the best clinical response in the inflammatory diseases of the lower airways.**

Key Words:

Nebulizer, Corticosteroids, Aerosol therapy, Inhaled drugs.

Introduction

Over the past few decades inhaled corticosteroids have been used with success by physicians. Nebulization is a common method for generating medical aerosol and it is largely used by adults and children all over the world, particularly for asthma and COPD. In fact children and older patients may have difficulty with conventional inhalation devices and therefore they may benefit from the easy-to-use delivery mechanism of the nebulizer.

Although little is known about the importance of the nebulizer characteristics to perform a correct nebulization, there are several studies that address this finding.

In a retrospective cohort study Marcus et al. showed that older patients, who used nebulized inhaled corticosteroids persistently, reported fewer emergency department visits and systemic corticosteroid use than before nebulized inhaled corticosteroids use. These improved outcomes were not associated with an increase in health care costs[1].

These observations have lead to prefer, in some patients, the nebulizers to perform aerosol therapy.

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Critical issue is related to the particle size generated (aerosol characteristics), the nebulization time and the drug output.

It is important to underline that, among nebulizers, poor performing nebulizers may not be able to generate a sufficient amount of aerosolized particles able to reach the lower airways[2].

Required size for aerosolized particles to have a therapeutic significance is less than 5 μm. The size is inversely related to the flow rate of compressed gas trough the device. High pressure supply and consequently low nebulization time are recommended to increase patient compliance[3].

In this study we assessed possible significant differences of the parameters measured during nebulization of inhaled corticosteroids between several representative nebulizers: aerosol characteristics, output/minutes, nebulization time, and compressor pressures.

The main purpose of the study was to identify the better performing nebulizer for each inhaled corticosterid, and moreover to assess the potential granulometric variations of different devices used for nebulizing inhaled corticosteroids, in order to improve clinical efficacy of inhaled drugs.

Materials and Methods

All the measures were performed in the Aerosol Research Laboratory of our Clinic – Respiratory Diseases Unit, University of Rome "La Sapienza", Italy. Compressor and compressor/nebulizer pressures, nebulization time, output/minutes, and aerosol characteristics were measured.

Inhaled Corticosteroids

Four inhaled Corticosteroids available in Italy were analysed: Beclomethasone dipropionate (Clenil per Aerosol 800 mcg/2 ml – Chiesi Farmaceutici, Parma, Italy); Flunisolide (Nisolid 2 ML 2000 mcg – Chiesi Farmaceutici, Parma, Italy); Fluticasone propionate (Flixotide Nebules 0.5 mg/2 ml – GLAXOSMITHKLINE, Verona, Italy); Budesonide (Pulmaxan Aerosol 0,5 mg/ml – ASTRAZENECA, Basiglio, MI, Italy).

All tested drugs were supplied by manufacterer as monodose vials.

Nebulizers

Four types of jet nebulizers, chosen out of the most used in Italy, were evaluated in the study (Table I). Three nebulizers for each type were tested for the analysis, for a total of 12 compressors/nebulizers. All nebulizers were filled with 2 ml of drug. The unit Clenny is composed by a specific ampoule created for its compressor. Compressors and nebulizers were bought from four commercial sources.

Aerosol Characteristics

Measuring aerosol particle size of nebulizers is confusing. For aerosol particle size many different results are possible from the same nebulizer, depending on the measurement method used. Over the past 50 years researchers have not naturally regressed to a commonly accepted nebulizer test method. Cascade impactors can drastically distort the aerosol size by causing full evaporation of the nebulized aerosol. Laser diffraction size measurement of aerosol particles cannot take into account droplet evaporation. In our study aerosol particle size produced by the nebulizers was measured with a high resolution instrument (Aerosizer Mach 2; API, Amherst, MA).

The Aerosizer is a time of flight aerosol beam spectrometer (TOFABS), an high resolution instrument that does not apply mathematical functions or corrective parameters established by the user and that is traceable with different standards[4].

Table I. Compressor and Nebulizer brand evaluated.

Compressor/Nebulizer brand	Type	Manufacturer	Location
Clenny/Clenny	Pneumatic	MEDEL	Parma, Italy
Turbo Boy/LC Plus	Pneumatic	PARI GmbH	Starnberg, Germany
Maxaer/	(Compressor)	ARTSANA	Como, Italy
Sidestream	Pneumatic	Medic-Aid Ltd.	Romedic-Meersen, The Netherlands
Nebula Nuovo/MB5	Pneumatic	MARKOS MEFAR	Bovezzo (BS), Italy

The TOFABS measurement method consists of (1) allowing a sample aerosol to undergo expansion through a nozzle into a vacuum chamber, such that each particle acquires a terminal velocity depending on its aerodynamic size, then (2) measuring the terminal velocity by determining the time taken for each particle to traverse a laser beam of fixed width. An experimental calibration curve relating time-of-flight and aerodynamic size, based on the use of polystyrene latex spheres, is shown to be in good agreement with a theoretical calibration obtained from the gas-particle dynamics equations.

The Aerosizer is capable of sizing several thousand particles a second, making it possible to obtain aerodynamic particle size distributions in a few seconds compared with up to 1 hour per measurement using compendial methods that are based on either the multistage liquid impinger or cascade impactor.

We performed the quality control testing on the Aerosizer with a standard NIST/BCR (polystyrene latex spheres, certified particle size standard; Duke Scientific Corporation, Palo Alto, CA) and obtained excellent repeatability of the results. The Aerosizer was set to measure the particles over a broad dynamic range (0.2 to 700 μm). The following variables was estimated: mass median aerodynamic diameter (MMAD: the particle diameter about which 50% of the mass of the aerosol particles is distributed.); geometric standard deviation (GSD: the spread of particle sizes); percentage of particles with an aerodynamic diameter less than 5 μm and 2 μm. The aerosol characteristics where evaluated for each minute of nebulization (3 analisys/min. for each single device and for a total of 252 granulometric measurements) until there was no visible or audible evidence of nebulization. The mean room temperature (± SD) over the study period was 25 (± 2.4) °C and the mean relative humidity was 42 (± 2.0) %.

We defined respirable particles as 1 to 5 μm for purposes of describing nebulizer performance. The same particle size range was used by other to describe nebulizer performances[2,5].

Evaluation of Nebulization Time and Aerosol Available to the Patient

Nebulization time (252 analyses) was determined by a stopwatch and was considered complete when there was no visible or audible evidence of nebulization for a period of 30 sec. The mass of the emitted drug was determined gravimetrically. The nebulizer was weighted (Gibertini Balance, Bologna, Italy) three times for each step: empty, after it was filled with medication (2 ml), for each minute of nebulization and at the end of the trial, for a total of 360 analyses. The percentage of solution that was nebulized was calculated from these mass values.

Compressor and Compressor Plus Nebulizer Pressure

The compressor and compressor plus nebulizer pressure was measured using a PARI PG 101 (PARI GmbH-Starnberg, Germany) pressure testing device (operating pressure: 200-1800 mbar ± 12 mbar). Three analyses were made for each minute of the estimated nebulization time for a total of 252 measurements for the compressors and 252 mesurements for the unit compressor plus nebulizer.

Stastical Analysis

Data were analyzed statistically using Statgraphics Plus software (Statistical Graphics Corp., Manugistics, Rockville, MA). ANOVA was performed to verify whether or not there were any significant differences between groups. Statistical significance was set at $p < 0.05$. Results are given as mean ± SD.

Results

Compressor and Compressor Plus Nebulizer Pressures

In Figure 1 were reported the nebulization pressures (mbar) of the different compressors and compressor/nebulizers.

Clenny showed the lowest pressure (551.18 ± 20 mbar), whereas Nebula the highest one (1329.35 ± 26.6 mbar). All the compressors, except for Clenny, exceeded 1100 mbar. Mean Pressures in mbar were respectively 551.18 (Clenny), 1161.18 (Turbo Boy), 1126.98 (Turbo Boy + LCp), 1197.8 (Maxaer), 1159.95 (Maxaer + Sid), 1329.35 (Nebula), 1305.33 (Nebula + MB5). One-way analysis of variance reported a significant difference between the tested devices ($p < 0.0001$).

Evaluation of Nebulization Time

Nebulization Time is the needed time (minutes) for each compressor to nebulize 2 mg of 4 different inhaled corticosteroids: beclomethasone

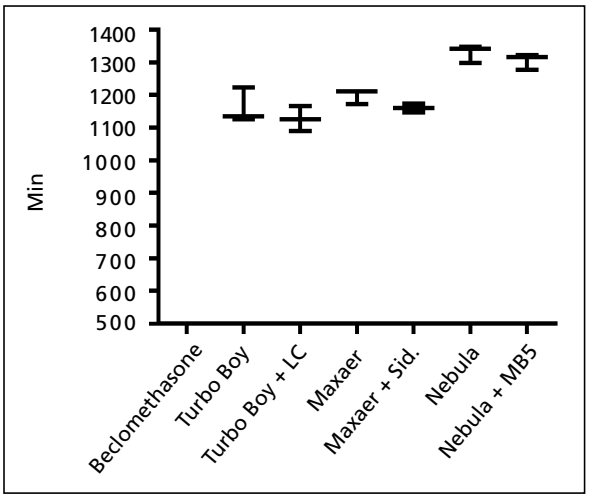

Figure 1. Compressor and compressor/nebulizer pressures. Clenny showed a significant lower pressure than other compressors. ANOVA $p < 0.0001$

dipropionate, flunisolide, fluticasone propionate and budesonide. Analysis of Nebulization Time showed a significant difference between nebulizer and inhaled corticosteroid for Clenny, Turbo Boy, and Maxaer, whereas it was not significant for Nebula. Data on nebulization Time were reported in Figures 2, 3, 4, and 5.

Maxaer showed the faster nebulization time than others, and Turbo Boy the higher time for each inhaled corticosteroid (Table II).

Available Aerosol to the Patient

Analysis of quantity (mg) of inhaled drug for each minute of nebulization showed a more available inhaled corticosteroid to the patient for Beclomethasone dipropionate and Budesonide with the tested nebulizers than other inhaled corticosteoids (Table III).

In the Figures 6, 7, 8, 9 were reported the nebulizer outputs (in mg) of the different corticosteroids for every minute of nebulization, until was no more visible or audible evidence of nebulization.

Table II. Nebulization Time (minutes) for 2 mg of different inhaled Corticosteroids and Nebulizers (Mean ± SD).

	Beclomethasone	Flunisolide	Fluticasone	Budesonide
Clenny	8.5 ± 0.6	10.7 ± 2.2	7.8 ± 1.6	7.7 ± 1
Turbo Boy + LCp	11.2 ± 1.5	12.5 ± 1.9	10.9 ± 1.2	10.3 ± 1.3
Maxaer + Sid.	5.25 ± 0.4	5.6 ± 0.3	4.6 ± 0.5	4.1 ± 0.1
Nebula + MB5	6.6 ± 0.7	7.8 ± 1.5	6.7 ± 1.8	7.2 ± 0.9

Table III. Drug Output in mg for each minute of nebulization.

	Minute	1	2	3	4	5	6	7	8	9
Beclomethasone	Clenny	0.33	0.66	0.98	1.3	1.54	1.67	1.77		
	Turbo Boy	0.31	0.64	1.1	1.29	1.42	1.5	1.57	1.61	
	Nebula	0.36	0.69	1.02	1.29	1.46				
	Maxaer	0.48	0.95	1.29	1.46					
Flunisolide	Clenny	0.33	0.2	0.41	0.6	0.78	0.96	1.13	1.26	1.37
	Turbo Boy	0.19	0.41	0.61	0.8	0.99	1.13	1.22	1.28	
	Nebula	0.22	0.43	0.62	0.76	1.05	1.12	1.19	1.24	
	Maxaer	0.47	0.89	1.19	1.4	1.4				
Fluticasone	Clenny	0.37	0.73	1.06	1.33	1.47	1.56			
	Turbo Boy	0.36	0.7	1	1.19	1.31	1.41	1.43		
	Nebula	0.32	0.62	0.87	1.06	1.23	1.34			
	Maxaer	0.52	1	1.3	1.44					
Budesonide	Clenny	0.32	0.65	0.99	1.28	1.46	1.62	1.75		
	Turbo Boy	0.32	0.61	0.9	1.15	1.35	1.47	1.55	1.57	
	Nebula	0.32	0.59	0.84	1.05	1.19	1.3	1.74		
	Maxaer	0.48	0.94	1.27	1.42					

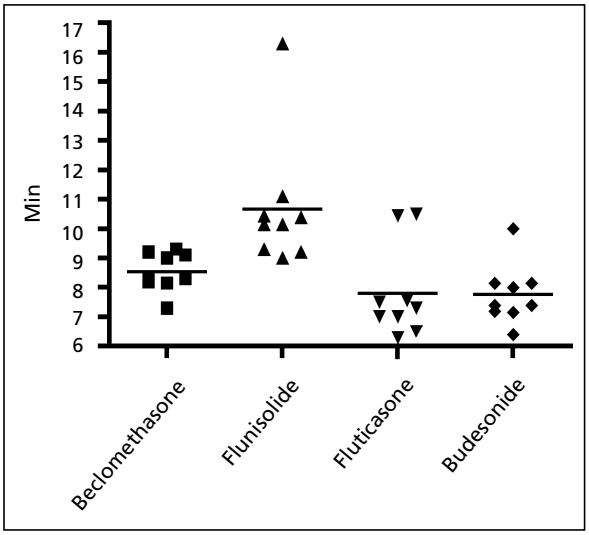

Figure 2. Clenny: nebulization time with different inhaled corticosteroids. ANOVA between inhaled corticosteroids $p = 0.0006$. Direct statistical comparisons showed: Beclomethasone vs Flunisolide $p = 0.0286$, Beclomethasone vs Fluticasone $p = 0.2048$, Beclomethasone vs Budesonide p 0.0170, Flunisolide vs Fluticasone $p = 0.0017$, Flunisolide vs Budesonide $p = 0.0113$, Fluticasone vs Budesonide $p = 0.9509$.

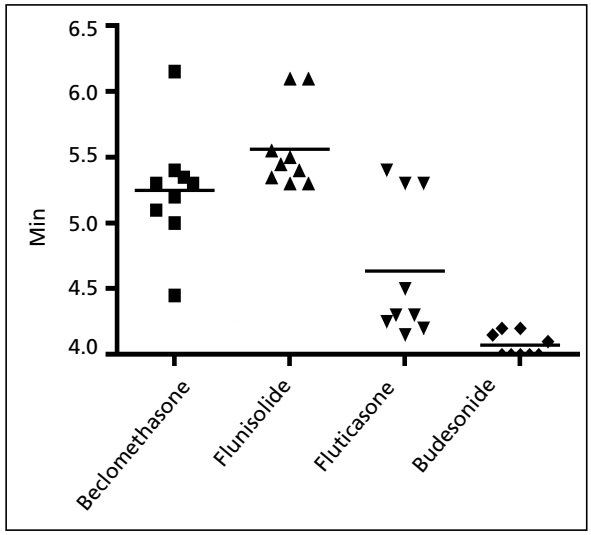

Figure 4. Maxaer: nebulization time with different inhaled corticosteroids. ANOVA between inhaled corticosteroids $p < 0.0001$. Direct statistical comparisons showed: Beclomethasone vs Flunisolide $p = 0.1167$, Beclomethasone vs Fluticasone $p = 0.0220$, Beclomethasone vs Fluticasone $p = 0.0220$, Flunisolide vs Fluticasone $p = 0.0054$, Flunisolide vs Budesonide $p < 0.0001$, Fluticasone vs Budesonide $p = 0.0149$.

Aerosol Characteristics

Twenty sputtering events of ampoule were reported with Turbo Boy nebulizer during nebulization of flunisolide. Five sputtering events were reported with Maxaer nebulizer during nebulization of fluticasone propionate. Nebula nebulizer reported 12 sputtering events during nebulization of flunisolide and 16 events during nebulization of fluticasone propionate. No sputtering event was reported for Clenny. Therefore, we ex-

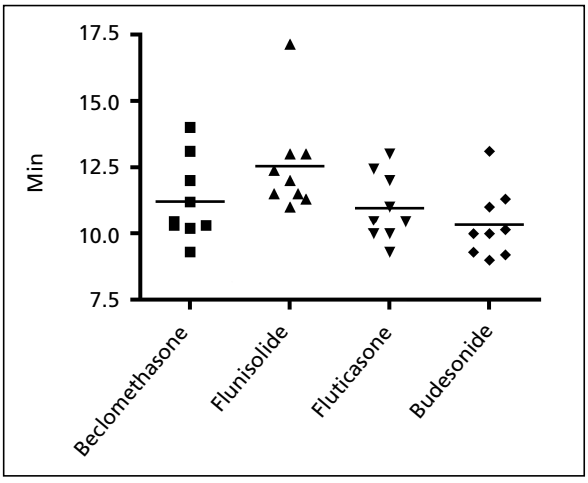

Figure 3. Turbo Boy + LCp: nebulization time with different inhaled corticosteroids. ANOVA between inhaled corticosteroids $p = 0.0298$. Direct statistical comparisons showed: Beclomethasone vs Flunisolide $p = 0.1351$, Beclomethasone vs Fluticasone $p = 0.7577$, Beclomethasone vs Budesonide $p = 0.3088$, Flunisolide vs Fluticasone $p = 0.0287$, Flunisolide vs Budesonide $p = 0.0337$, Fluticasone vs Budesonide $p = 0.2919$.

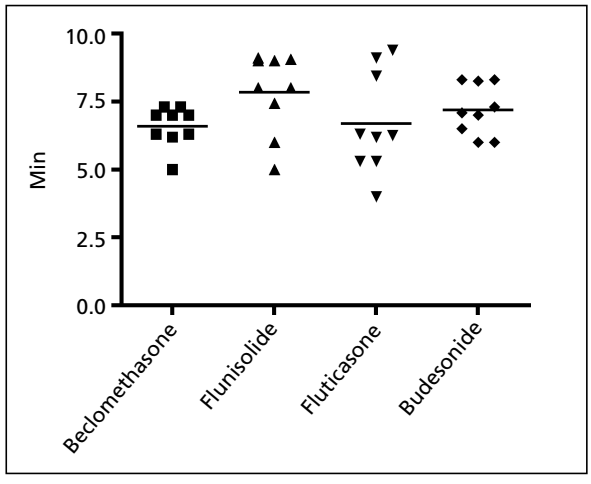

Figure 5. Nebula + MB3: nebulization time with different inhaled corticosteroids. ANOVA between inhaled corticosteroids $p = 0.1979$. Direct statistical comparisons showed: Beclomethasone vs Flunisolide $p = 0.0488$, Beclomethasone vs Fluticasone $p = 0.8681$, Beclomethasone vs Budesonide $p = 0.0427$, Flunisolide vs Fluticasone $p = 0.1309$, Flunisolide vs Budesonide $p = 0.2659$, Fluticasone vs Budesonide $p = 0.2131$.

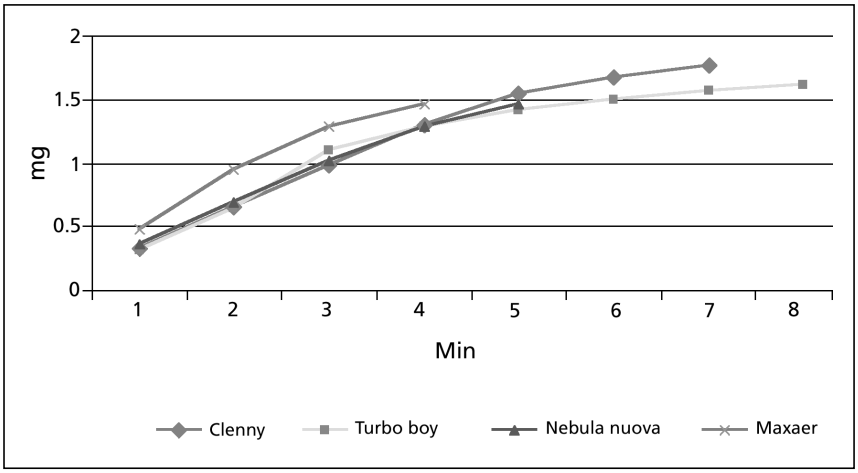

Figure 6. Nebulizer output with beclomethasone dipropionate $p < 0.0001$.

cluded sputtering events in the statistical analysis and in figures of granulometrical measures. In Figures 10, 11, 12, 13 were reported MMAD of specific corticosteroids with the different nebulizers. All tested aerosols were heterodispersed (GSD > 1.22).

MMAD of all inhaled corticosteroids showed significant differences among the four nebulizers ($p < 0.0001$). The MMAD of Beclomethasone dipropionate was 2.65 ± 0.2 (Clenny), 3.34 ± 0.5 (Turbo Boy), 3.15 ± 0.8 (Nebula), 2.46 ± 0.2 (Maxaer); for Flunisolide it was 1.98 ± 0.3 (Clenny), 4.89 ± 2.7 (Turbo Boy), 4.4 ± 2.9 (Nebula), 2.27 ± 0.5 (Maxaer), showing a significant high value of mean and SD with Turbo Boy and Nebula. For Fluticasone the MMAD was 2.65 ± 0.2 (Clenny), 2.29 ± 0.1 (Turbo Boy), 2.38 ± 0.5 (Nebula), 1.87 ± 0.3 (Maxaer). Lastly, for Budesonide it was 2.43 ± 0.2 (Clenny), 2.17 ± 0.2 (Turbo Boy), 1.92 ± 0.2 (Nebula), and 1.52 ± 0.1 (Maxaer).

Percentage of particles < 5 μm e < 2 μm of different corticosteroids obtained from the four nebulizers showed a significant statistically difference ($p < 0.0001$). These data were reported in Figure 14 and 15.

Discussion

In Italy nebulizers account for around 50% of prescriptions of drugs to be inhaled, particularly corticosteroids, mucolytics, β2-agonists, and anticholinergic drugs[6].

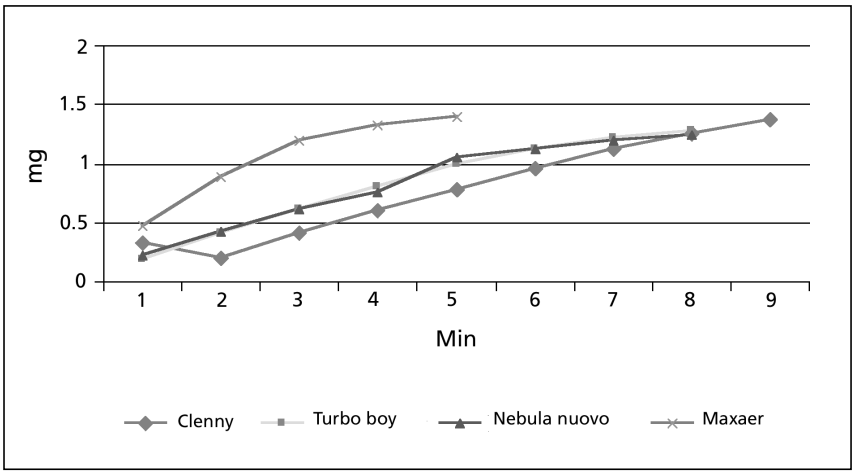

Figure 7. Nebulizer output with flunisolide ($p = 0.0002$).

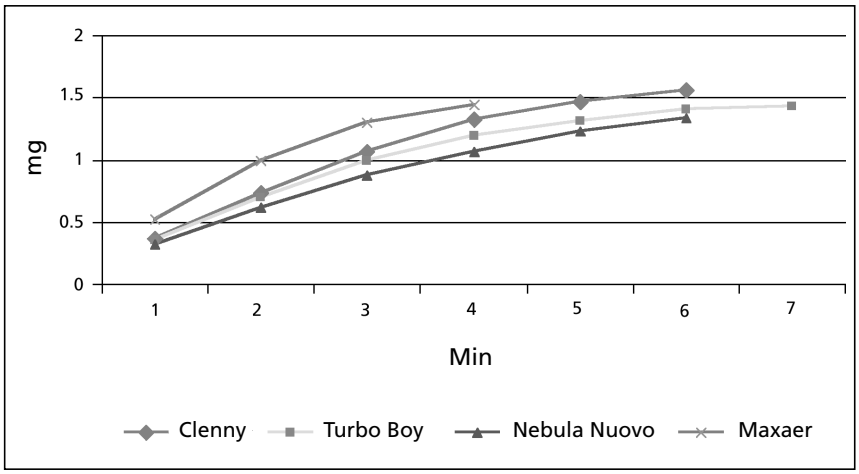

Figure 8. Nebulizer output with fluticasone propionate ($p < 0.0001$).

This is the first study that compare the most frequently used compressors/nebulizers and all inhaled corticosteroids available for nebulization in Italy.

Inhaled corticosteroids are the most potent and effective therapy for treating many respiratory diseases. We studied four inhaled corticosteroid products: beclomethasone dipropionate, flunisolide, fluticasone propionate and budesonide. They differ in potency; however, clinical efficacy is similar when equipotent doses are administered[7-11].

A variety of factors influence product selection and patient response, including the therapeutic ratio, pharmacokinetic properties, and the inhalation delivery device[12].

In order to properly work, an inhaled drug must reach an "*effective*" distribution in the area to be treated.

The efficacy of nebulizer therapy is influenced by a great number of factors, including the design of the device and the characteristics of the drug solution/suspension.

Two main parameters are generally used to evaluate the performance of nebulizers: the particle size distribution of the aerosol and the drug output rate. The particle size distribution and the drug output rate are basically determined by the design and user conditions of the nebulizer.

The choice of the type of nebulizer for nebulization of a certain drug solution may initially be based on laboratory evaluation. The major part of the mass or volume distribution should preferably correspond with aerodynamic particle diameters in the range of 1 to 5 micrometer. The intended drug output must be realized with-

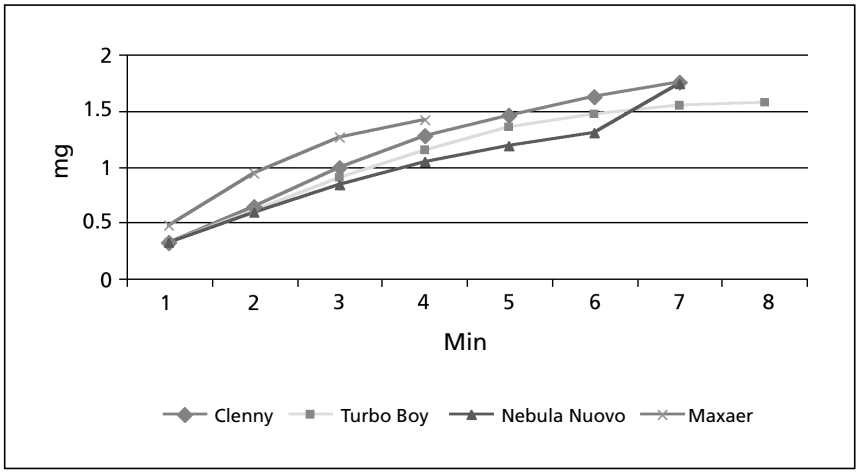

Figure 9. Nebulizer output with budesonide ($p < 0.0001$).

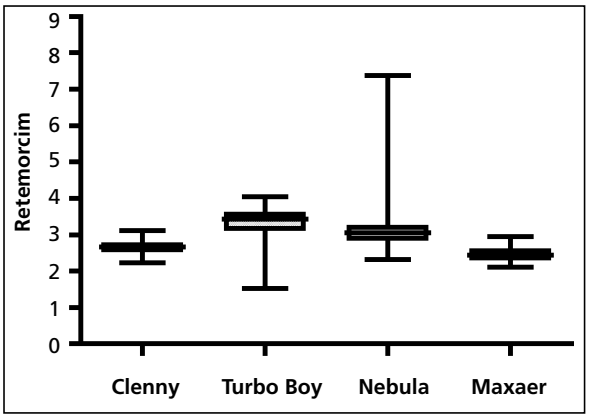

Figure 10. MMAD of beclomethasone dipropionate with different nebulizers ($p < 0.0001$).

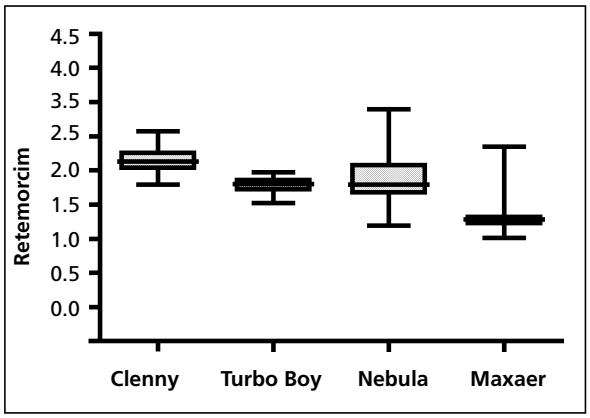

Figure 12. MMAD of fluticasone propionate with different nebulizers ($p < 0.0001$).

in a reasonable nebulization time (dependly on the amount of drug put in the nebulizer).

Moreover mechanical properties of nebulizers are likely to change during use. An average utilization time of nebulizers is not available. Therefore, the performance of nebulizers should be checked periodically[13].

Particle size is often the most important criterion upon which the unit compressor/nebulizer is based.

In this respect, the results of aerosol therapy are deeply influenced not only by the traditional physical, pharmacokinetic and pharmacodynamic properties of the drug, but also by the suitability of the delivery system and its correct use by the patient.

The interest of a comparison among the various models of nebulizers lies on the fact that their different aerosol producing systems and the different materials of their ampoules can influence their therapeutic efficacy. The type of nebulizer can determine, in fact, the percentage of solution actually nebulized, the quantity of aerosol generated per unit time and the aerodynamic characteristics of the aerosol[2,14-24].

Although these characteristics are largely influenced by the commercial model of the nebulizer and the type of drug to be aerosolized.

The results obtained through pneumatic nebulizers themselves depend on the driving gas flow rate of the compressor and the kind of material the ampoules are made of[17-19]. For instance, glass ampoules, due to possible manufacturing faults, produce a less regular nebulization (with frequent phenomena of sputtering) whereas polycarbonate ampoules usually guarantee a better nebulization[6].

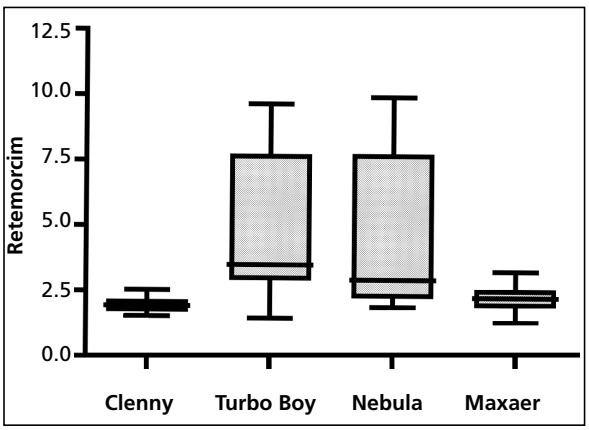

Figure 11. MMAD of flunisolide with different nebulizers ($p < 0.0001$).

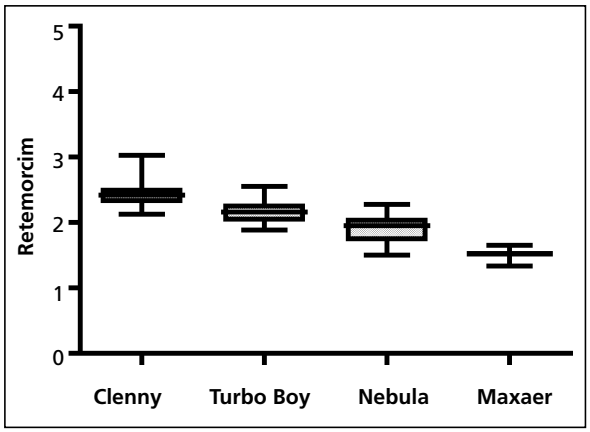

Figure 13. MMAD of budesonide with different nebulizers ($p < 0.0001$).

At present there is no accepted uniform method regarding bench testing of nebulizers. As a result, in vitro, the performance of any given instrument may vary depending on the method used[25-27].

Performance of Nebulizers

Although it is current opinion that performance of nebulizers is marginally important, in this study we demonstrated that an interdevices variability exist in nebulization of tested drugs. It is essential to know, before prescription, the nebulizer showing the best performance with the specific inhaled drug to use. In this way we'll obtain the best drug deposition in the lower airways and a more therapeutic efficacy.

The particle size distribution of the aerosol and the drug output rate determine the performance of nebulizers. However, it should be taken into account that the performance of the nebulizer is also influenced by patient related factors[3,15].

It is difficult to compare particle sizing results from different studies. The set up of the equipment, the measuring equipment and its software, the characteristics of the drug solution/suspension and the compressor used are all factors that affect the final result.

In our study we observed several sputtering events during the nebulization of flunisolide and fluticasone propionate, whereas no sputtering events were observed with beclomethasone dipropionate and budesonide.

Compressor/Nebulizer Pressures

Although compressor/nebulizer pressure of Clenny device was significantly lower (551.18 mbar) than other nebulizers (> 1100 mbar), it was optimal to guarantee the best performances with tested drugs (Figure 1).

Nebulization Time

A disadvantage can be a longer nebulization time required to aerosolize the solution. In clinical practice a nebulization time of 15 to 30 minutes is acceptable. Longer period will compromise the patient's compliance[13].

Our data showed nebulization times suitable for allowing a good patient's compliance, even if significant differences were observed in nebulization time of different drugs and nebulizers (Table II and Figures 2, 3, 4, and 5).

Drug Output

The drug output rate is another important factor to compare nebulizers. For delivery of a high dose to the lungs, nebulizers with a high output rate are preferred in order to confine the nebulization time. The output of nebulizers can be described by the aerosolized volume or the aerosolized mass of drug. The output rate is defined as the mass of drug converted to aerosol per unit time. The nebulized volume can be determined simply by weighing the nebulizer before and after use. Results may be misleading because they do not take into account the increase in drug concentration within the nebulizer caused by evaporation of the solvent. Therefore drug output rate in mg/min is a better parameter for the nebulizer output[13].

From the drug output only a minor fraction will be deposited in the lung. The relation between in vitro and in vivo deposition is only partly understood and to date it has not been possible to predict drug delivery only from in vitro studies on nebulizers. Therefore, studies in patients should be performed before a drug solution/suspension for nebulization can be recommended for clinical practice. The mechanical properties of nebulizers are likely to change during use, so the performance of nebulizers should be checked periodically[13].

The output characteristics of commercial nebulizers vary greatly and will impact on the time required for treatment as well as the total amount of drug delivered to the lungs. Gravimetric methods can be used as simple and convenient screening techniques for comparing jet nebulizers under a wide range of experimental conditions[28].

This study confirmed a significant difference in the output of nebulized drugs through the compressors/nebulizers tested, as other studies demonstrate with other drug/device combinations [5], and that correct matching of nebulizer and compressor is important to achieve the optimal performance of the system (Figures 6, 7, 8, and 9).

Aerosol Characteristics

To achieve a therapeutic effect, particles of nebulized drugs should have an MMAD of less than 5 µm.

In this study the results showed significant ($p < 0,0001$) differences among the compressors/nebulizers used (Figures 10, 11, 12, and 13). All tested aerosols were heterodispersed (GSD > 1.22). The optimal particle size required to maximize the therapeutic ratio of a molecule may be different for a β2-agonist than for inhaled corticosteroid. If we understand better this relationship, we will achieve specific drug targets with future inhalers[29].

Therefore, current devices have different lung deposition profiles that could affect clinical efficacy when devices are switched. Devices that achieve for the inhaled drug an high ratio lung to systemic are preferable[15,30-32].

Moreover we evaluated, in this study, the percentage of particles in the respirable range < 5 μm and those < 2 μm delivered from the different devices.

Concerning beclomethasone dipropionate, all devices delivered a high percentage (about 90%) of particles < 5 μm (Figure 14), whereas with flunisolide only Clenny (98.8%) and Maxaer (96.3%) delivered particles < 5 μm in high percentage, opposed to Turbo Boy + LC Plus nebulizer (28%) and Nebula Nuovo + MB5 nebulizer (45.5%).

Relating to fluticasone propionate, Clenny (98%), Turbo Boy + LC Plus nebulizer (99.1%), and Maxaer with Sidestream nebulizer (86%) delivered a high percentage of particles < 5 μm, contrary to Nebula Nuovo + MB5 nebulizer (55.3%).

Finally, all devices were able to deliver a high (> 90%) percentage of particles < 5 μm of budesonide.

Since the small airways have a greater surface area than large airways and are exposed to a variety of disease processes, we studied the percentage of delivered particles < 2 μm (Figure 15) to evaluate the particles able to reach the small airways, an highly important target in the anti-inflammatory therapy of many pulmonary diseases.

Small-airway disease is a significant component of obstructive airway pathology. COPD classically involves the terminal bronchioles, but increasingly there is recognition that asthma, and particularly chronic persistent asthma, also involves the small airways[33-35].

There are reasons to believe that these small particles (< 2 μm) may also be helpful for treatment of infants. Small particles are likely to bypass the nose and to be deposited in the lungs compared with larger particles[32].

In our study Clenny (34.8% and 60%) and Maxaer + Sidestream nebulizer (40.6% and 59.8%) revealed to be the more efficient devices able to deliver a high percentage of particles < 2 μm respectively with beclomethasone dipropionate and flunisolide, in opposition to Turbo Boy + LC Plus nebulizer (21.6% and 9.8%) and Nebula Nuovo + MB5 nebulizer (26.9% and 20.1%).

Moreover, Maxaer + Sidestream nebulizer (55.2%) and Turbo Boy + LC Plus nebulizer (47.3%) delivered a significant higher percentage of particles < 2 μm of fluticasone propionate than Clenny (36.4%) and Nebula Nuovo + MB5 nebulizer (24.9%).

Lastly, Maxaer + Sidestream nebulizer (83.3%) and Nebula Nuovo + MB5 nebulizer

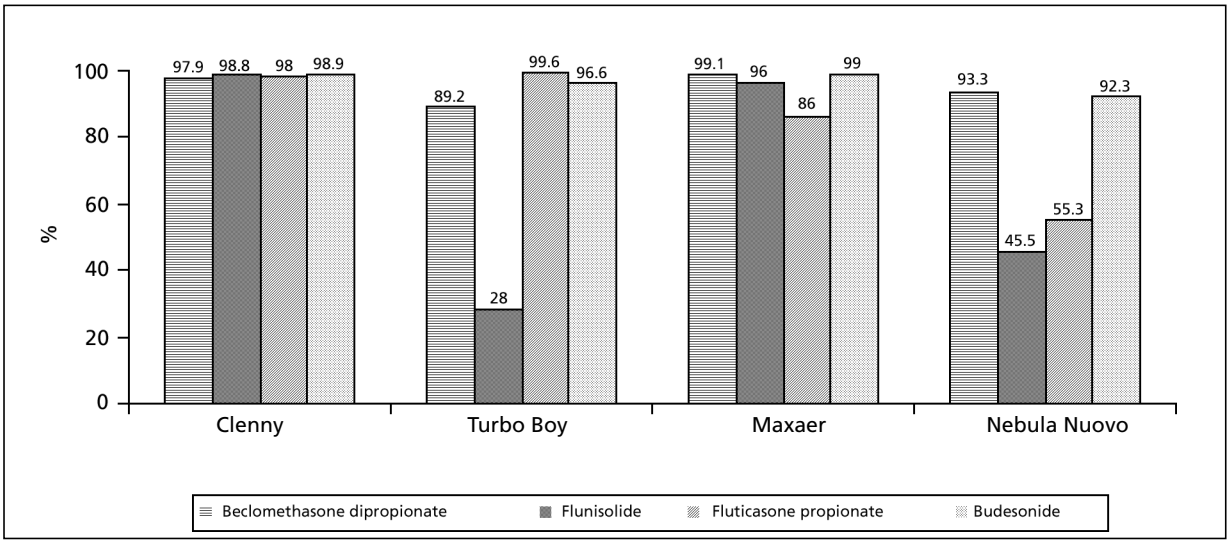

Figure 14. Percentage of particles < 5 mm ($p < 0.0001$).

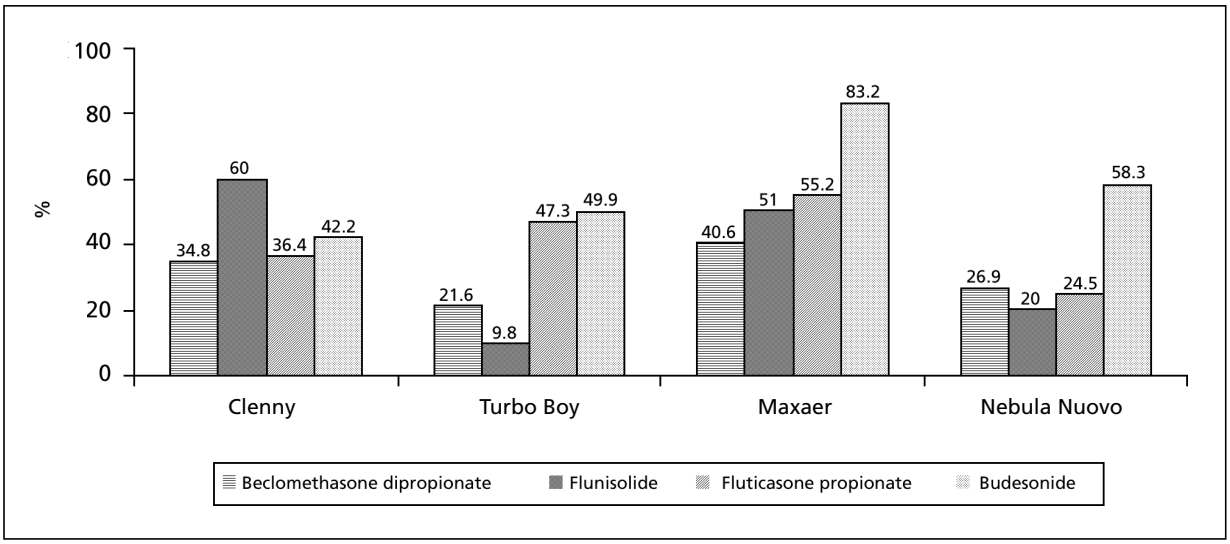

Figure 15. Percentage of particles < 2 mm ($p < 0.0001$).

(58.3%) delivered a significant higher percentage of particles < 2 μm of budesonide than Turbo Boy + LC Plus nebulizer (49.9%) and Clenny (42.2%).

Conclusions

Our results suggest that tested compressors/nebulizers would deliver different masses of corticosteroids to the lungs. This may have important consequences in determining the efficacy and side effect profile of this drugs. Moreover, in this study, the assessed nebulizer/compressor combinations showed considerable variation in overall performance.

In the past many studies have used saline solutions, water or tracer materials to evaluate nebulizer performances. As demonstrated in recent reports, nebulizer performance is affected by the solution/suspension used. For these reasons our results should not be extrapolated to drug solution/suspension other than beclomethasone dipropionate, flunisolide, fluticasone propionate and budesonide for nebulization.

Our results have important clinical and research implications. The most important determinant of aerosol delivery during nebulizer therapy is the specific nebulizer brand used. When nebulizers are used for research application, the nebulizer characteristics must be evaluated and reported for the conditions used in the investigation[2].

In this study we demonstrated the evidence that, when inhaled corticosteroids are used, the compressor/nebulizer unit can make the therapeutic difference.

So, when we want to obtain effective clinical responses aimed to resolve the different inflammatory diseases of the lower airways, the device has the same importance of the drug.

Since the aim of inhalation therapy is the deposition of particles in the respiratory tract to be treated, the results of this study may also be useful to find out optimum conditions in cases of therapeutic applications.

In conclusion, our study demonstrated that there is a wide variation in performance of nebulizer/compressor combinations tested with nebulized corticosteroids, and that correct matching of the nebulizer/compressor is important to ensure optimum performance.

Moreover with nebulizers, as observed by Hess et al.[2], the approval process for the delivery device is separate from the approval process for the drug. Further, the approval process for nebulizers does not require demonstration of a physiological response. As we have demonstrated in the present study, the aerosol characteristics, the nebulization time and the dose delivered can vary among the tested nebulizers.

Clinical comparisons are necessary to determine if these differences affect substantially clinical outcomes[7-11], as Terzano at al. demonstrated in a previous study[6].

We look forward nebulizers to be submitted to "*medical devices*" regulatory authorities, particularly in Italy where they are largerly used.

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