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Effectiveness of beclomethasone dipropionate aerosolized through different nebulizers to asthmatic patients

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Abstract. – **The aim of our study was to verify if the type of nebulizer used could influence the results of aerosol therapy with beclomethasone dipropionate (BDP) in mild allergic asthma. We assigned 27 asthmatics allergic to grasses to 3 groups and treated them from May to July 1998 with aerosol therapy with BDP (800 µg) b. i. d. via nebulizer + pMDI salbutamol (200µg) if necessary. Each group used a different type of nebulizer: jet nebulizer with glass ampoule (group JG); jet nebulizer with polycarbonate ampoule (group JP); ultrasonic nebulizer (group US). During the study patients underwent periodic lung function tests and methacholine bronchial challenges, recorded twice a day self-monitoring PEF and filled out a daily diary for the presence and intensity of asthmatic symptoms. At the end of the study the provocative dose of methacholine causing a 20% fall in FEV_1 (PD20), the self-monitoring PEF and the clinical scores were all greatly improved, but without any statistically significant difference among the three groups. On the contrary, the variations during the study of basal spirometric parameters (specifically FEV_1, PEF, FEF_{25}) were significantly better in jet nebulizer groups than in group US. The results coming from the aerosol characterization that we carried out for each of the three nebulizers confirmed the clinical findings, since jet nebulizers showed greatly lower MMAD than the ultrasonic nebulizer (2.9 and 3.7 vs 5.8). Our data suggest that jet nebulizers are more appropriate than ultrasonic nebulizers for delivering BDP in aerosol therapy.**

Key Words:

Aerosol therapy, Nebulizers, Beclomethasone dipropionate, MMAD, Asthma

Introduction

Over the past few decades aerosol therapy has become one of the major treatments in many different lung diseases.

Drugs dispensed in aerosol sprays are commonly delivered through pressurized metered dose inhalers (pMDI), dry powder inhalers (DPIs) or nebulizers. The latter are 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, particularly asthma and COPD. In Italy, nebulizers account for around 50% of prescriptions of drugs to be inhaled, particularly corticosteroids.

In order to properly work, an inhaled drug must reach an "effective" distribution in the area to be treated. 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[1,2].

The quality and the appropriateness of drug delivery have been considered for the last years a topic factor for the success of inhalation therapy in asthma[3,4]. Therefore, many investigators have compared the efficacy of different drug delivery systems (such as inhalers vs nebulizers) in asthma therapy[5,6] or they have evaluated the potential improvement related to the use of new tools (such as spacers)[7-10]. Nevertheless, a comparison between the clinical efficacy of different models of the same delivery system is rarely carried out, especially for nebulizers. Moreover studies comparing different nebulizers often consider pathologies other than asthma[11-14], include bench tests rather than clinical data or concern nebulizers sharing the same aerosol producing system[18-20].

The interest of a comparison among the various models of nebulizers lies on the fact that their different aerosol producing systems (jet or ultrasonic) and the different materials of their ampoules (glass or polycarbonate) 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.

Specifically, ultrasonic nebulizers might alter complex molecules[21,1] and are characterized by MMAD generally higher than those produced by pneumatic nebulizers[22,17], 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[16,17,23] and the material the ampoules are made of. For instance, glass ampoules, due to possible manufacturing faults, produce a less regular nebulization (with frequent phenomena of *splluttering*) whereas polycarbonate ampoules usually guarantee a better nebulization[1].

Several studies including a clinical comparison in asthmatics between jet and ultrasonic nebulizers evaluated the bronchodilator response to nebulized albuterol[24,25]. However there is a lack of studies comparing the clinical efficacy of long-term steroid-based aerosol therapies delivered through jet or ultrasonic nebulizers.

Such a comparison is even more interesting considering that glucocorticoids can be prepared as respiratory suspension and it has been proved that suspensions are more difficult to nebulize than solutions and should not be aerosolized through ultrasonic nebulizers[26,15,21].

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[27]. This variability points out the utility of using both granulometric and clinical data in the same study.

However, the results of a clinical trial can be affected by the large inter-patients variability of anthropometric characteristics (such as the morphology of the respiratory system) and individual ventilatory parameters during aerosol therapy that can influence the distribution and deposition of the drug in the airways[21]. To control, at least partly, this variability a careful program of patient's education and supervision should always be included in such clinical studies.

The aim of our study was to verify if the type of nebulizer used (jet with glass ampoule, jet with polycarbonate ampoule or ultrasonic) could influence the results of the aerosol therapy with beclomethasone dipropionate (BDP) in mild allergic asthmatics carefully trained to correctly perform the treatment.

Material and Methods

Total patients

In May 1998 we enrolled 27 asthmatic outpatients at the University Institute of Respiratory Diseases in Milan (18 patients) and at the Respiratory Allergy and Pneumology Unit in Bergamo (9 patients). Inclusion and exclusion criteria are summarized in Table I.

Among the 27 patients (17 males and 10 females; mean age 29.1 ± 11.6 yrs) 9 subjects had FEV_1 or the ratio $FEV_1/FVC < 80\%$ of the predictive values[28] at basal lung function test in visit 0 with a reversibility of at least 15% and at least 200 ml after the inhalation of salbutamol 200 mcg and they did not undergo the methacholine bronchial challenge test. The other 18 patients with normal basal lung function test showed a provocative dose of methacholine causing a 20% fall in FEV_1 (PD20) < 750 γ at the bronchial challenge test with methacholine.

Bi-stratified randomization

The patients were distributed into 3 groups (JG, JP, US) by means of a bi-stratified randomization according to the respiratory functional status (either $FEV_1 < 80\%$ or positive methacholine challenge test) and to the occurrence of asthmatic symptoms (either seasonal in spring-summer or perennial with relapses during this season). Any other variable, including gender and age, was distributed at random. Table II summarizes the features of the patients as a whole and in each group.

Table I. Inclusion and exclusion criteria for the enrollment in the study.

Inclusion cristeria	Exclusion criteria
• Males or females aged ≥ 14 years old. • FEV_1 or the ratio $FEV_1/FVC \leq 80\%$ of the predictive values at the basal Respiratory Functional Test with a reversibility of at least 15% and at least 200 ml after the inhalation of salbutamol 200 mcg OR • Provocative dose of methacholine causing a 20% fall in FEV1 (PD20) ≤ 750 γ at the Methacholine Challenge Test. • Skin prick test (SPT) positive for Graminae Mix (wheal for grasses large at least μ of the histaminic wheal). • Asthmatic symptoms (dyspnoea, cough, wheezing) present either exclusively during spring-summer (April-July) or constantly with acute relapses during that period of time*. • Signed Informed Consent.	• Use of systemic steroids or regular use of pulmonary topic steroids, DSCG, nedocromil sodium or chetotifen. • Presence of contraindications for the use of pulmonary topic steroids. • Severe asthma for which the topic BDP + salbutamol treatment is insufficient. • Signs of restrictive syndrome at the Respiratory Functional Tests. • Presence of clinical and/or functional signs of BPCO. • Presence of lung cancer, TB, sarcoidosis, interstitial lung disease or other lung pathologies which may influence the results of the study. • Current Immunotherapy. • Certain or presumed pregnancy. • Breast-feeding. • Poor compliance to the therapy or to the study. • Refusal to give Informed Consent.

* This criterion refers to the clinical relevance of skin sensitization to grasses taking the pollen calendars of these plants in northern Italy into account.

The patients were treated 9 weeks, from May to July, by aerosol-therapy with 800 μg beclomethasone dipropionate (2 ml BDP suspension + 1 ml NaCl 0.9% solution) twice a day via nebulizer + pMDI salbutamol (200 mg) if needed.

Each patient was given a brand new nebulizer for his/her personal use. Three different kinds of nebulizers were used and all the patients belonging to the same group used the same commercial model according to the following scheme:

- Group JG: jet nebulizers with glass ampoule (Microlux model; Medel; Parma, Italy)
- Group JP: jet nebulizer with polycarbonate ampoule (Nebula Nuovo model; Mefar; Bovezzo, Brescia, Italy)
- Group US: ultrasonic nebulizer (Universal II model; FLAEM Nuova; Brescia, Italy)

Educational program

According to the aim of the study, a carefully defined, correct and complete

Table II. Clinical characteristics of the total patients and of the three groups JG, JP and US. Letter "p" refers to the statistical comparison JG *vs* JP *vs* US.

	Group JG	Group JP	Group US	p	Tot group
N°	9	9	9		27
Males/females	6/3	4/5	7/2		17/10
Mean age (years)	27.1	32.3	28.0	NS	29.1
Age range (years)	17-51	23 - 62	14-53		14-62
Mean length asthma (yrs)	13,4	11,7	9.6	NS	11,6
Patients with rhinitis	8	9	7		24
Mean sensitiz. index*	0.304	0.387	0.338	NS	0.343
Patients sensitiz. to mites	4	5	4		13
Patients with $FEV_1 \leq 80\%$	3	3	3		9
Patients with PD20 < 750 γ	6	6	6		18
PD20 average (γ)	346.74	292.38	365.42	NS	332.19

*Number of positive allergens/number of tested allergens.

Table III. Procedures carried out in each visit.

	Visit 0	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6
Physical examination	•	•	•	•	•	•	•
Skin Prick Test	•						
Informed Consent	•						
Basal Spirometry	•		•	•	•	•	•
Methacholine Challenge Test*	•		•	•	•	•	•
Educational Program		•					
Supply of nebulizer		•					
Supply of peak flow meter		•					
Supply diary		•	•	•	•		

*Only if basal FEV_1 and ratio FEV_1/FVC > 80% of predictive values.

training program in accordance with the recent guidelines of the Società Italiana per gli Aerosol in Medicina was implemented[29].

In particular the patients were instructed about the preparation of the mixture BDP+NaC10.9%, the use of the open-lips nozzle and the nose-clip, the correct breathing pattern (slow tidal breathing, short pause at the end of inspiration, occasional deep breaths and quick exhalation), the accurate maintenance of the instrument[30,31]. At the end of visit 1 the patients underwent the first aerosol therapy session under the supervision of the researcher. For all technical problems concerning the use of nebulizers the patients were asked to refer only to the researcher.

Daily diary and peak flow meter

In visit 1 each patient was given and taught to use a peak flow meter. At every visit a daily diary was distributed.

In the diary patients recorded twice a day clinical scores (in a 0:3 scale) of their dyspnea and cough symptoms, the occurrence and the amount of salbutamol spray use, the occurrence of any side effect and the best of three PEF values recorded by means of self-monitoring Peak Flow meters.

Visits

After the enrollment (visit 0), patients underwent periodic visits for 9 weeks according to the following scheme:

Procedures carried out in each visit are summarized in Table III.

Particle sizing experiments

An Aerosizer Mach2 was used (Amherst Process Instruments Inc, Amherst-MA) for the aerosol characterization of the particles delivered by each of the three devices. The characterization study of the particles was carried out at the ambient temperature equivalent to 25° C with a relative humidity of 50%.

Pollen count

A daily count of the main pollens (grasses and Parietaria) from the beginning of May to the end of July in Milan was available and is summarized in Figure 1.

Statistical analysi

Differences between pairs of mean were investigated by means of t Student test, while the one-way ANOVA was applied to evaluate differences between the per cent variations recorded at the end of the study in the three groups. The linear variation of specific parameters during the various visits of the

Times between the visit		As little as possible	2 weeks	2 weeks	2 weeks	2 weeks	2 weeks
	Visit 0	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6
						optional	24
Attending patients	27	27	27	24	24	10	24

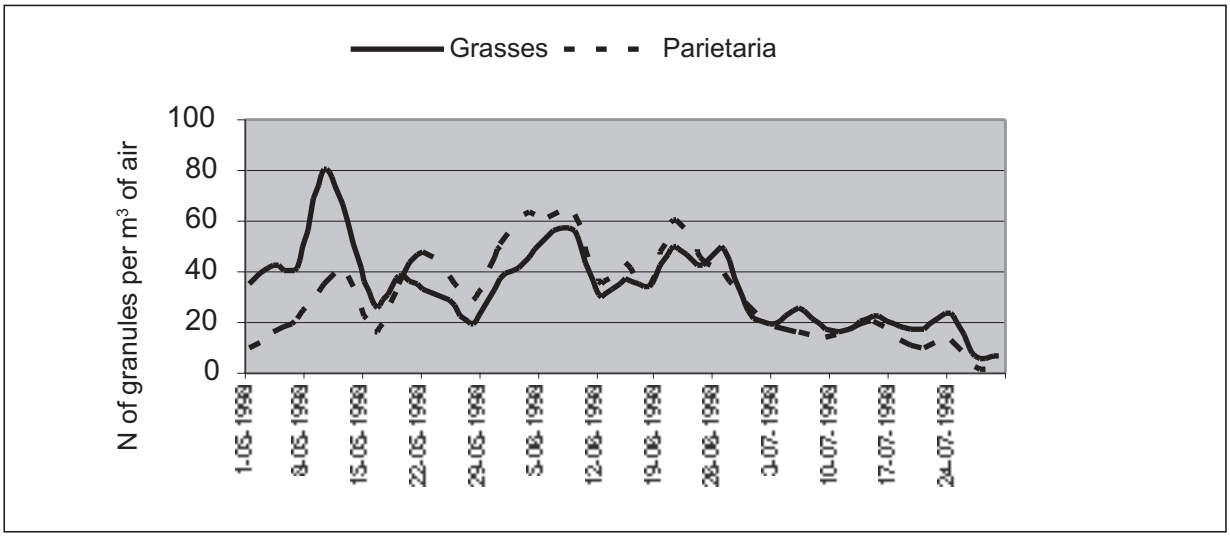

Figure 1. Pollen count of the principal regional pollens (grasses and Parietaria) during the study period (thanks to the kind collaboration of *Laboratorio Farmaceutico Lofarma s.r.l., Milano, Italy*).

study was investigated by means of the Spearman's Rank Correlation Coefficient. The χ^2 test was used to detect differences among proportions. A $\alpha = .05$ level of significance was chosen for all the tests.

Results

Three patients were no longer willing to participate to the study after visit 2. They were excluded from all the data processing.

Spirometric parameters

In the first part of Table IV the mean per cent variations during the study of spirometric parameters (FEV_1, PEF and FEF_{25}) respect to the value recorded in visit 0 are summarized for all the patients and compared among the different groups. For each analysis only patients with a basal value of the specific parameter in visit 0 lower than 90% of the predictive value were considered.

By considering the patients as a whole, both FEV_1 and PEF, unlike FEF_{25}, proved to significantly and linearly improve during the study. By analyzing the different groups, none of the spirometric parameters showed significant linear variations in group US, whereas FEV_1 in group JP, FEF_{25} in group JG and PEF in both the groups significantly improved by a linear trend.

By considering the final per cent variations at the end of the study respect to visit 0 (Figure 2 and Table IV), both FEV_1 and FEF_{25}, unlike PEF, showed significant differences among the groups. For all the parameters Group US had lower final values than jet nebulizers.

PD20

In the second part of Table IV the mean percent variations during the study of PD20 respect to visit 0 are showed for all the patients and the different groups. There is a significant linear increase both for all the patients and for every group, but the final percent variations do not show significant differences among the various groups.

Figure 3 shows the mean percent variations during the study of PD20 for all the patients and for the subgroups of patients sensitized also to mites and patients not sensitized to mites. Although the improvement of PD20 was earlier in the subgroup not sensitized to mites, at the end of the study the two subgroups had very similar final per cent variations of PD20.

Self-monitoring PEF and Symptoms clinical scores

At the ninth week self-monitoring PEF values showed a final 13% improvement respect to the first week (significant linear improvement during the study: $p < 0.0005$). Similarly at the ninth week dyspnea symp-

Table IV. Mean percent variations (respect to Visit 0) of spirometric parameters and PD20 recorded during the study among all the patients and in the various groups.

	Visit 2	*Visit 3*	*Visit 4*	*Final Visit*	*Spearman**	*ANOVA***
FEV_1 total patients	6.1%	2.7%	6.2%	8.1%	< 0.005	
FEV_1 Group JG	7.5%	3.8%	6.8%	11.0%	NS	
FEV_1 Group JP	9.4%	10.3%	10.7%	15.0%	< 0.0005	< 0.05
FEV_1 Group US	4.5%	-7.7%	1.0%	-3.3%	NS	
PEF total patients	16.5%	15.1%	20.0%	26.3%	0.0000	
PEF Group JG	8.8%	8.3%	11.1%	21.5%	< 0.005	
PEF Group JP	32.4%	30.2%	35.9%	43.3%	< 0.005	NS
PEF Group US	10.2%	8.3%	14.0%	13.6%	NS	
FEF_{25} total patients	1.7%	2.4%	5.9%	12.9%	NS	
FEF_{25} Group JG	0.7%	19.5%	19.6%	54.0%	< 0.01	
FEF_{25} Group JP	1.2%	-4.8%	-1.7%	0.0%	NS	< 0.05
FEF_{25} Group US	3.3%	-7.5%	-1.8%	-15.4%	NS	
PD20 total patients	127.3%	164.7%	250.4%	270.2%	0.0000	
PD20 Group JG	139.4%	114.2%	268.4%	371.7%	< 0.05	
PD20 Group JP	134.6%	178.1%	270.0%	253.2%	< 0.0001	NS
PD20 Group US	104.8%	196.3%	205.0%	192.5%	< 0.01	

* P value for the Spearman's rank correlation coefficient: it tests the null hypothesis that there is no linear variation of the specific parameter during the study.
** P value for one-way analysis of variance: it tests the null hypothesis that there is no difference among the three groups in the per cent variations of the specific parameter at the end of the study.

toms had decreased by 65%, cough symptoms by 100% and use of salbutamol by 75%. All these three parameters improved by a highly significant linear trend during the study (p = 0.0000). However none of them showed any significant difference among the groups at the end of the study.

Particle sizing experiments

The aerosol characterization is summarized in Table V. Jet nebulizers (particularly the one with polycarbonate ampoule) showed better values than the ultrasonic nebulizer for every parameter considered.

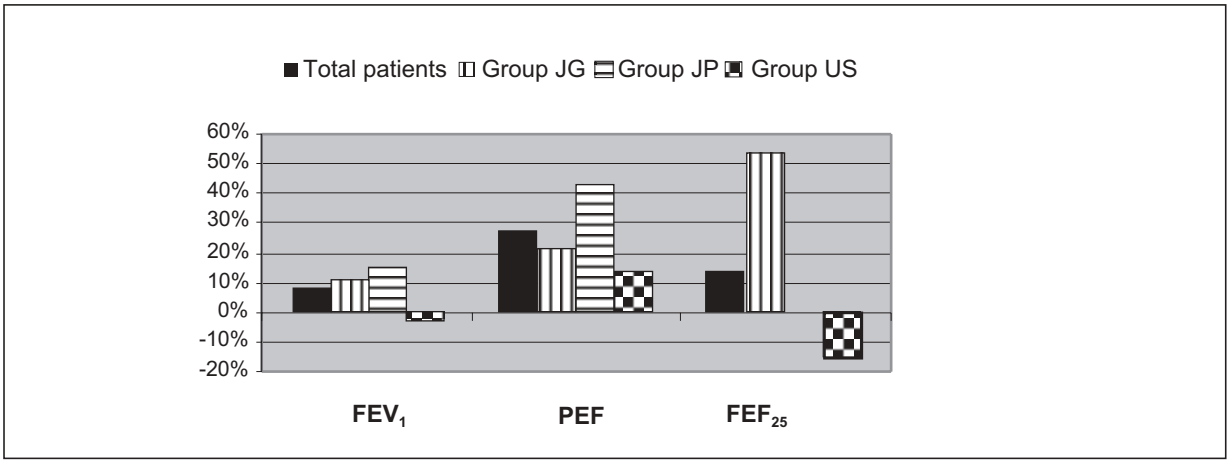

Figure 2. Mean per cent variations of spirometric parameters at the end of the study respect to Visit 0 for all the patients and the single groups. Only patients with a basal value of the specific parameter in visit 0 lower than 90% of the predictive value were considered.

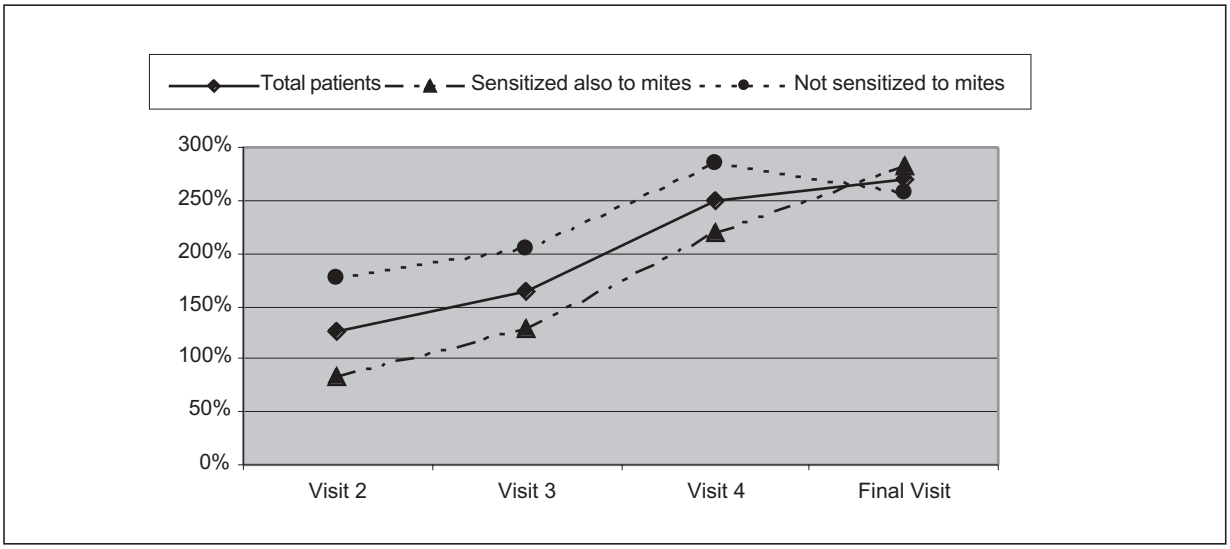

Figure 3. Mean percent increase of PD20 during the study for all the patients and for the subgroups of patients sensitized also to mites and patients not sensitized to mites.

Discussion

Ours should be considered a pilot study, since the small sample size does not guarantee a complete control of the wide inter and intra-individual variability. Nevertheless, our data suggest that the selection of the nebulizer is able to influence the efficacy of BDP aerosol therapy in mild allergic asthma.

By considering the patients as a whole, all the parameters considered showed a significant linear improvement during the study, with the only exception of FEF_{25}. It is likely that this improvement was partly due to the gradually decreasing grasses pollen exposure during the study period (Figure 1). However, all the patients were polysensitized and, among them, 13 subjects showed also a clinically relevant sensitization to mites whose concentration is presumed not to have relevantly varied during the study. This subgroup did not show any reduction in final PD20 improvement respect to the other patients.

By comparing the results obtained in the different groups, jet nebulizers proved to induce a higher final improvement of FEV_1 and FEF_{25} values than ultrasonic nebulizers. They also showed, unlike ultrasonic nebulizers, a statistically significant linear increase of PEF values during the study. Ultrasonic nebulizers never showed a significant relationship (neither positive nor negative) between therapy duration and variation of any spirometric parameter.

On the contrary, the percent increase of PD20 was significant for all the groups, but there was no statistically significant difference among their final percent variations. Similarly, self-monitoring PEF and clinical scores improved in all the groups and did not show any significant difference among the groups at the end of the study.

Therefore, in our study spirometric parameters appeared more sensitive than bronchial hyperresponsiveness, clinical scores or self-monitoring PEF in detecting potential differences in the clinical efficacy of nebulizers. This conclusion may be related to several factors.

First, clinical scores and the necessity of salbutamol use, unlike spirometric parameters, largely depend on the patient's perception of the disease and they can be influenced by psychological elements. Secondly, it is pos-

Table V. Aerosol characterization of the three nebulizers.

Nebulizer	*MMAD*	*GSD*	*% < 5*	*% < 2*
Microlux (JG)	3.7	1.4	84.2	7.6
Nebula Nuovo (JP)	2.9	1.4	93.7	9.5
Universal II (US)	5.8	1.9	34.9	0.4

MMAD= Mass Median Aerodynamic Diameter (μm); GSD = Standard geometric deviation; %< 5 = particles percentage smaller than 5 μm; %< 2 = particles percentage smaller than 2 μm.

sible that the variability in efficacy among the nebulizers lead, among the patients, just to subclinical differences that can be detected only by instrumental examinations rather than patient-based reports.

Thirdly, despite the careful educational program, self-monitoring PEF can be still affected by the patient's skills. The capability and the willingness of correctly using the peak flow meter are assumed to be randomly distributed among the groups, but they could still confound the actual effect of the therapy. The presence and supervision of the researcher during a spirometric test are usually able to better control this inter-subject variability and this could also explain why the spirometric PEF showed a higher improvement than the self-monitoring PEF in our study.

Finally and more interestingly, the differential response of the parameters could be related to how the size of the aerosolized particles and the location of their targets in the airways match.

In our aerosol characterization jet nebulizers showed low MMAD (3.7 for JG and 2.9 for JP). On the contrary, the ultrasonic nebulizer's particles had MMAD twice larger than JP. A large percentage of the particles aerosolized by jet nebulizers were smaller than 5 mcg (respirable fraction: 84.9% for JG and 93.7% for JP). This percentage was only 34.9% for the ultrasonic nebulizer, whereas a 50% respirable fraction has been proposed as minimum standard for nebulizers[2,21]. Similarly, almost 10% of the particles from JP were smaller than 2 mcg, while the percentage was virtually null for the ultrasonic nebulizer.

The different characteristics of the particles aerosolized by the three nebulizers can influence a differential deposition of the drug into the airways. In particular, smaller nebulized particles can reach target cells and receptors localized more peripherally along the airways.

In this respect PD20 could be less sensitive to the granulometric characteristics of the nebulizers because of the proximal position of the muscarinic receptors[32]. On the contrary, spirometric parameters, such as the flow at low lung volume (FEF_{25}), could be more affected by the component from the small airways and require smaller aerosolized particles to be modified. Consequently, they could be more likely to reveal differences in the therapeutic efficacy among the nebulizers.

Although it has been proved that also the severity of asthma can influence the level of deposition of nebulized beclomethasone along the airways[33], the stratified randomization should have controlled this potential confounding effect in our study. Moreover, results from the aerosol characterization and the clinical trial were concordant and predictive of each other in our study.

Few previous studies failed to show significant clinical differences between jet and ultrasonic nebulization[24,25]. However, they focused on the bronchodilator response to beta-agonist rather than the long-term therapy with steroids.

Our results confirm that, although findings are related to the specific commercial models used[2], granulometric characteristics of aerosolized steroid suspensions are better for jet nebulizers than ultrasonic ones and that steroid suspensions should not be aerosolized through ultrasonic nebulizers. Jet nebulized BDP proved to be efficacious in positively influencing even very sensitive parameters.

We can conclude that the aerosol producing system influences the granulometric characteristics and even some elements of the clinical efficacy of aerosolized BDP and that jet nebulization seems the most appropriate. Our data stress the importance of more extensive studies and, eventually, guidelines on this topic.

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