Acceptability, preference, tolerance and clinical efficacy of dipropionate beclomethasone delivered by two inhalation devices in chronic asthma patients: Clenil Pulvinal versus Miflasona Aerolizer

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Background: Approximately half of all asthmatic patients adhere to their prescribed treatment regimen, which makes noncompliance with treatment one of the main problems associated with the disease. It is possible that inhalation devices combining technological advances with comfort and simplicity of use could increase treatment compliance.

Objective: To compare the acceptability of and preference for two inhalation devices (Pulvinal and Aerolizer), as well as to evaluate the efficacy of and tolerance for beclomethasone dipropionate when delivered by these two systems.

Method: A multicenter, randomized, crossover parallel study was carried out involving 83 patients with stable asthma. Patients received 500-1000 mg/day of beclomethasone dipropionate. After a 2-week run in, the patients were randomized to begin a 4-week crossover treatment period with equivalent doses of Clenil Pulvinal® (CP) or Miflasona Aerolizer® (MA).

Results: Both groups showed improvement in dyspnea and FEV_1, and acceptability was considered good or excellent in both groups. Of the patients studied, 50.6% preferred CP, and 39% preferred MA. In their future treatment regimes, 54.5% would choose the CP and 37.7% the MA.

Conclusion: Clinical efficacy and acceptability were comparable between CP and MA.

Key words - Asthma/therapy. Beclomethasone/ administration & dosage. Randomized controlled trials. Treatment Outcome.

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INTRODUCTION

Although the understanding of the pathogenesis of asthma has improved and great investments have been made in the search for new medications, controlling this disease still appears to be problematic worldwide. Various explanations have been proposed, some related to treatment costs, others related to lack of awareness – on the part of health professionals and patients alike – of the clinical and psychosocial aspects of asthma as a chronic disease.

Noncompliance with treatment or incorrect use of inhalation devices may have a significant negative impact on the effectiveness of treatment. Giraud and Roche showed that the incorrect use of metered-dose inhalers is related to worse asthma control due to decreased efficacy of the inhaled corticosteroids (ICs). The authors reported that asthma instability score, based on daytime and nocturnal symptoms, beta$_2$-agonist usage, and emergency room visits, as well as global perception of asthma control, were significantly higher in the group of patients who did not use ICs properly[1].

Since drugs have a direct action on respiratory mucosa, inhalation allows the therapeutic effect to be achieved with smaller doses, as well as reducing adverse effects[2], which has made inhalation the principal means of administering asthma medications. A growing number of inhalation devices have now been developed in an attempt to improve pulmonary deposition efficacy and comfortable use. The ideal device should be easy to use, have low production costs and be designed in such a way that they can be customized to meet the specific needs of each patient, thereby improving the effectiveness of the treatment. Despite the importance of seeking medication and device alternatives that patients will find more acceptable, there are very few studies – and none in our milieu – that have focused on patient preference for one inhalation device over another.

The objective of this study was to evaluate the use and handling of two easy-to-use, inexpensive systems (Pulvinal and Aerolizer) as for the acceptability of and preference for these devices. Secondarily, the efficacy of and tolerance for beclomethasone when delivered by these two systems were also evaluated in the control of chronic asthma. Although the understanding of the pathogenesis of asthma has improved and great investments have been made in the search for new medications, controlling this disease still appears to be problematic worldwide. Various explanations have been proposed, some related to treatment costs, others related to lack of awareness – on the part of health professionals and patients alike – of the clinical and psychosocial aspects of asthma as a chronic disease.

METHOD

A multicenter, randomized, crossover parallel study was carried out. At six health care centers, non-smoking patients, ranging from 18 to 65 years of age, diagnosed with asthma at least one year prior and clinically stabilized (for at least 2 consecutive months) with constant daily doses of ICs (500-1000 mg of beclomethasone or equivalent doses of other corticosteroids), were included. The size of the sample was not based on conventional statistical calculations since, by the time the present study was planned, no studies evaluating rates of patient acceptability of inhalation devices had been published. As for efficacy, data collected from the sample were sufficient for the comparison of the same medication used in two different dry-powder systems. The crossover study design allowed patients to be used as their own controls, thereby enhancing homogeneity of the responses.

Patients were only allowed to use short-acting inhaled beta$_2$-agonists for symptom relief during the study. Patients using fluticasone, oral bronchodilators, systemic corticosteroids, and leukotriene antagonists were excluded from the study, as were pregnant or breastfeeding women and women who did not use appropriate contraception. Patients with a history of cardiovascular, renal, neurologic, hepatic, or any other severe disease, as well as those who were known to be intolerant to the medications used in study, were also excluded. All patients gave written informed consent approved by the research ethics committees of the hospitals involved in the study. The present study received financial support from Farmalab-Chiesi do Brasil.

Protocol: Patients selected for study were included in a 2-week run-in period, during which the medication in use was maintained. Patients were subsequently included in the treatment period. Patients not allowed to enter the subsequent

treatment phase were those who presented changes in inhaled corticosteroid dose, use (for two consecutive days) of short-acting inhaled beta$_2$-agonist doses 50% higher than the normal dose or night waking due to an asthma attack (for two consecutive nights or for two out of three nights), as well as those requiring treatment with oral or systemic corticosteroids. Patients were randomized to begin the first 4-week treatment period with doses of either Clenil Pulvinal or Miflasona Aerolizer that were equivalent to the daily dose they had been receiving prior to the study. Immediately after this first treatment period, patients began another 4-week period using the alternate treatment.

During every visit, patients were submitted to clinical evaluation and spirometry, and pharmacodynamic tests were performed. In addition, the occurrence of adverse episodes and changes in the therapeutic regimen were determined during the visits. Diurnal and nocturnal symptoms, the use of relief medication and 3 measurements of peak expiratory flow taken upon waking and prior to sleeping were reported in a symptom diary. The evaluation of the intensity of signs and symptoms was based on a scale from 0 to 3 (absent, mild, moderate and severe) for the following parameters: dyspnea at rest, exercise-induced dyspnea, cough at rest, cough due to stress, and crackling sounds during auscultation. The use of short-acting inhaled beta$_2$-agonists and the number of diurnal and nocturnal bronchospasm episodes were also recorded.

After each treatment, patients and examiners gave their opinion on the acceptability of the system used, and examiners gave their opinion on the efficacy and tolerability of the device used. At the end of the study, patients and examiners gave their opinion regarding acceptability, and patients expressed their preference between the two systems used.

Statistical analysis: For comparison of demographic and physical examination data between groups, we used the Student's *t*-test. For simultaneous comparison of mean values of spirometry results between groups and within each group, we used two-way ANOVA. We used The chi-

TABLE 1
Patient characteristics

	Groups:	*A-P*	*P-A*	comparison
		(n = 41)	(n = 42)	between groups
Age	mean ± SD	35.1 ± 12.2	37.1 ± 12.4	n.s.
(years)	range	18 - 63	18 - 64	
Gender	male	10 (24.4%)	6 (14.3%)	n.s.
	female	31 (75.6%)	36 (85.7%)	
Race	Caucasian	35 (87.5%)	33 (78.6%)	
	African	2 (5.0%)	7 (16.7%)	n.s.
	Mixed	3 (7.5%)	2 (4.7%)	
Asthma	up to 5 years	17 (43.6%)	25 (62.5%)	
duration	6 - 20 years	8 (20.5%)	8 (20%)	n.s.
(years)	+ 20 years	14 (35.9%)	7 (17.5%)	
Measured FEV_1	mean ± SD	2.7 ± 0.8	2.6 ± 0.8	n.s.
After bronchodilator use	range	0.91 – 4.32	0.43 – 4.04	
(liters)				
Predicted FEV_1	mean ± SD	3.1 ± 0.7	2.9 ± 0.5	n.s.
After bronchodilator use	range	1.92 – 4.57	1.91 – 4.09	
(liters)				

FEV_1= forced expiratory volume in 1 second, A-P = Aeroliser – Pulvinal,
P-A = Pulvinal – Aeroliser, n.s. = not significant

square test was used for the comparison of demographic data and the evaluation of acceptability, tolerability, and global evaluation between groups. In addition, Friedman's test was used to compare clinical parameters between visits, and we used the Mann-Whitney test for the comparison of clinical parameters between groups. Statistical significance was set at 5%, and all tests presented normal distribution of data.

RESULTS

The study comprised 83 patients, allocated at random into two groups: 41 patients in the Miflasona Aerolizer – Clenil Pulvinal group (A-P group) and 42 patients in the Clenil Pulvinal – Miflasona Aerolizer group (P-A group). Two patients were excluded from the study due to asthma exacerbations and the use of unauthorized medication. In relation to the demographic data, both groups were homogeneous (Table 1).

Clinical evaluation: At the study onset, 13 patients in the P-A group and 16 patients in the A-P group presented diurnal symptoms. There was no difference in diurnal and nocturnal symptoms between the two groups. Throughout the study, a significant reduction in exercise-induced dyspnea was observed in both groups (group P-A: pre-treatment score = 0.9, after P = 0.7 and after A = 0.5; group A-P: pre-treatment score = 0.8, after A = 0.5 and after P = 0.4; $p < 0.001$). Two patients presented adverse effects (dysphonia and oral candidiasis) during the treatment with Clenil-Pulvinal, and no patients presented any adverse effects after the use of Miflasona Aerolizer. There was no difference regarding the use of short-acting inhaled $beta_2$-agonists.

Spirometry: When we compared the initial visit to subsequent visits during treatment (visits 3 and 4), we found a significant increase in mean FEV_1, although there was no difference between the groups. For visits 1, 3 and 4, this increase was seen prior to the use of the bronchodilator (2.3, 2.6, and 2.5, respectively, in the P-A group; 2.4, 2.6, and 2.7, respectively, in the A-P group; $p < 0.001$), as well as after the use of the bronchodilator (2.6, 2.8, and 2.7, respectively, in the P-A group; 2.7, 2.9, and 3.0, respectively, in the A-P group; $p < 0.001$). There was no statistically significant difference in peak expiratory flow between the groups.

Evaluation of inhalation system acceptability: Most patients considered both Pulvinal and Aerolizer quite easy to master, to reload, to inhale the medication from, and to visually inspect the medication (Figure 1). There was no statistically significant difference between groups. According to the examiner opinions, acceptability of the two inhalation systems was statistically similar in both groups, most examiners considering acceptability to be good or excellent (Figure 2).

Inhalation system preferences: There was a trend showing a preference for the Pulvinal system, although there was no statistical significance. Half of the patients (51%) preferred Pulvinal, whereas 39% preferred Aerolizer, and 10% stated no preference (Figure 3)

Inhalation systems of choice for patients: If patients were to maintain medication, Pulvinal would be the system of choice for 54.5%, Aerolizer for 37.7%, and only 7.8% indicated no preference (Figure 4).

Global evaluation of therapeutic efficacy: Most examiners considered therapeutic efficacy either good or excellent, and there was no statistically significant difference between the groups.

DISCUSSION

This study showed that beclomethasone, when administered through Pulvinal or Aerolizer devices, is an effective asthma treatment, and that there was no relevant difference in relation to the effectiveness of powder inhalation when using either device. Although patients suffered from clinically stable asthma when they were included in the study, an increase in FEV_1, which could be related to higher compliance to the treatment during clinical protocols, was observed after both treatments. However, the symptom score only improved after the second treatment with Pulvinal. This does not necessary mean a definite superiority of this device, since this was not observed after the first treatment. However, if we consider that a significant part of the group of patients had previously used the Aerolizer system, which could have favored the use of this medication since patients were accustomed to handling the device, we are likely to interpret that these findings as favorable to the Pulvinal system. However, other studies would be needed in order to confirm this

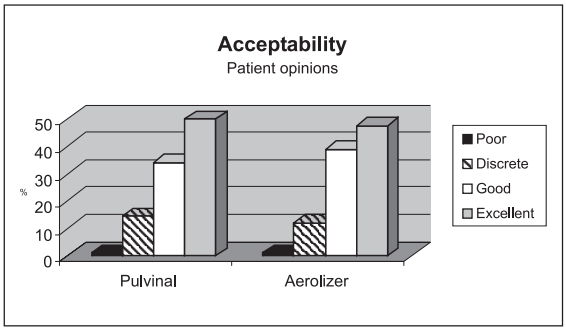

Figure 1. Patient acceptability of Pulvinal and Aeroliser (p NS)

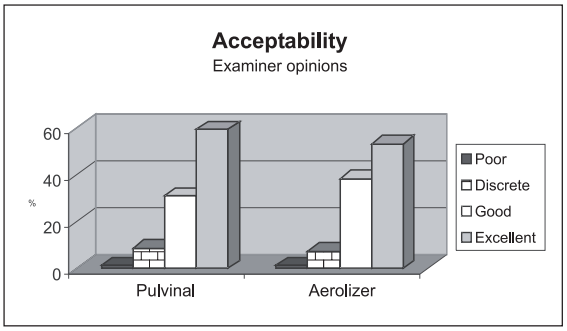

Figure 2. Acceptability of Pulvinal and Aeroliser as determined by the examiners (p NS)

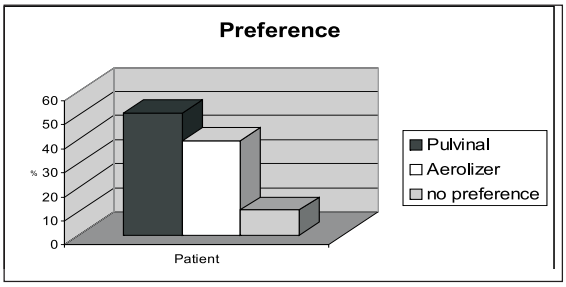

Figure 3. Patient preference in relation to the device used (NS)

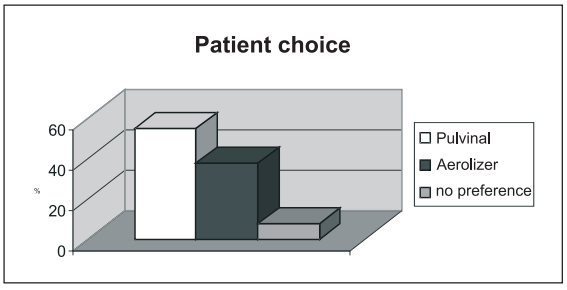

Figure 4. Patient inhaler of choice at the study endpoint

conclusion. In addition, some patients might have preferred Pulvinal because it is new, with the prospect of achieving improved results.

The study was designed in order to compare the preference for and acceptability of both systems, and the results show a tendency for patients to prefer Pulvinal, although there was no statistical significance. Short-term studies may not accurately reflect the impact of patient preference for and acceptability of a specific treatment. It seems reasonable to assume that the consequences would become more evident in direct proportion to the length of the treatment period employed.

Considering the severity of asthma and the need for long-term administration of inhaled corticosteroids, devices that combine technical advances with greater patient acceptability and preference may increase treatment effectiveness and minimize treatment noncompliance.

Although efficacious drugs for asthma control are available, long-term noncompliance with treatment[3-10], as in other chronic diseases, decreases the effectiveness of such treatments significantly, resulting in higher morbidity and mortality[11-13]. It is known that approximately half of the patients with asthma use the prescribed medication effectively[14-15], and there is a direct correlation between noncompliance with inhaled corticosteroid treatment and uncontrolled asthma[16].

In order to minimize this problem, specialists have put considerable emphasis on asthma education programs based on a plan of action administrated by the patients themselves. Such programs have been proven to improve asthma control, reducing hospitalizations, visits to emergency rooms, non-scheduled visits, the number of days missed from school and work, and nocturnal symptoms[17-18]. However, very few patients have access to asthma education programs. Studies have shown that only a small percentage of patients receive a written plan of action[19].

Although various factors, such as medication costs, fear of adverse effects, cultural or psychological aspects and factors related to doses and the administration of medications, have been recognized as potential reasons for treatment noncompliance, there have been very few studies evaluating patient preference for various inhalation devices. Nielsen et al., in a study comprising 274

asthmatic patients, evaluated which characteristics of inhalation devices patients considered most important and found that ease of reloading, durability and easy dose charging, as well as ease of handling and inhalation were considered the most important aspects[20].

The preference for a specific treatment seems to be linked not only to its therapeutic efficacy, but to cultural and personal issues as well. Weinberg et al.[21] reported that 70% of adolescent patients preferred oral zafirlukast, and only 27% preferred inhaled beclomethasone, which is a more efficacious medication. This is in accordance with other studies that have reported higher compliance with treatments involving oral medications[22,23].

In conclusion, the development of inhalation devices and inhaled medications that provide simplicity and comfortable use is an important objective in the management of asthmatic patients. The first step in prescribing inhalation devices is to test and compare these medications in order to verify their equivalence and efficacy. The second step is to evaluate individual patient preferences in order to increase compliance with the treatment and consequently achieve better control of the disease.

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