
Effects of salbutamol delivered by dry-powder inhaler on methacholine-induced bronchoconstriction*

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Background: Short-acting β_2 agonists delivered by metered-dose inhaler (MDIs) are the drugs usually used for the reversal of methacholine-induced bronchoconstriction. The β_2 -agonists that are delivered by dry-powder inhaler (DPI) can be an efficacious option.

Objective: To evaluate the effectiveness and speed of action of salbutamol delivered by DPI (Pulvinal; Butovent[®]), in comparison to salbutamol delivered by MDI, in reversing methacholine-induced bronchoconstriction.

Method: Sixty successive methacholine-induced bronchoconstriction patients who presented a decrease of at least 20% in forced expiratory volume (FEV₁) were evaluated prospectively. Of these 60 patients, we randomized 30 (first group) to receive 200 μ g of salbutamol by MDI and 30 (second group) to receive 200 μ g of salbutamol by DPI (Pulvinal). Both drugs were administered with the objective of reversing bronchoconstriction during the final phase of a bronchoprovocation test. The FEV₁ values obtained at one and five minutes after bronchodilator administration were evaluated.

Results: The groups were comparable in gender distribution, age, weight, dose level provoking a 20% drop in FEV₁ (first group: 1.3 mg; second group: 1.19 mg; $p = 0.79$) and post-methacholine FEV₁ (first group: 2.03 l; second group: 1.99 l; $p = 0.87$), with no statistically significant differences between the two groups. In the first group (MDI), the mean increase in FEV₁ was 16.2% (at one minute) and 22.2% (at five minutes), and in the second group (DPI) it was 17% (at one minute) and 23.6% (at five minutes). There was no statistically significant difference between the groups ($p = 0.8$).

Conclusion: The β_2 -agonists delivered by DPI (Pulvinal) present the same bronchodilator efficacy and speed of action as do those delivered by the more traditional MDI method.

Key words: Asthma. Bronchodilator agents/administration & dosage. Albuterol/administration & dosage. Methacholine chloride/administration & dosage. Respiratory therapy/methods. Administration, inhalation/methods. Prospective studies.

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INTRODUCTION

Asthma is a chronic inflammatory disease characterized by lower airway hyperresponsiveness and by variable airflow limitation that can resolve spontaneously or through treatment. Asthma is clinically characterized by recurrent wheezing, dyspnea and chest tightness, as well as coughing - at night and upon waking in the morning⁽¹⁾. According to data in the national and international literature, the prevalence of asthma, as well as the consequent morbidity and mortality, has been increasing^(2,3).

There are two basic treatments for asthma: rescue medications (so-called "quick-relief drugs", especially bronchodilators) and long-term control medications. Every regimen designed for patients with asthma includes bronchodilator therapy, either for simple relief of symptoms caused by bronchospasm or for reversal of severe bronchoconstriction in asthma attacks⁽⁴⁾. Short-acting β_2 -agonists in pressurized metered-dose inhaler (MDI) formulations are the drugs generally used for reversal of bronchoconstriction caused by exercise or by nonspecific factors. The use of beta-adrenergic bronchodilators via MDI guarantees rapid liberation of the active substance, providing multiple doses at low costs. However, the efficiency of, and side effects resulting from, inhaled formulations depend on the type of inhaler, the medication contained within and the adherence to usage guidelines (coordination, respiratory pattern, etc.). As a result, the response to the treatment may vary considerably⁽⁵⁾. Some patients, especially the elderly and children, may find it difficult to use MDIs properly, causing some reduction in In order to simplify the administration of inhaled bronchodilators, a series of dry-powder devices have been created. Administration of bronchodilators via dry-powder inhalers (DPI) is an efficacious option for the immediate reversal of bronchospasm. These devices release the dose through respiration, eliminating the necessity of synchronizing inhalation with actuation of the canister, as is the case with MDIs. With DPI devices, approximately 20% of the dose bronchodilator efficiency.

Abbreviations used in this paper:

DL₂₀ - Dose level provoking a 20 % drop in FEV₁
DPI - Dry powder inhaler
MDI - Metered-dose inhaler
PEF - Peak expiratory flow
SBPT - Sociedade Brasileira de Pneumologia e Tisiologia
FEV₁ - Forced expiratory volume in one second
FVC - Forced vital capacity
FEV₁/FVC - FEV₁ as a percentage of FVC (Tiffeneau index)

released is deposited in the lungs, whereas MDI devices deposit only 8% to 10% of the dose released⁽⁶⁾. When delivered via DPI, the effect of bronchodilators and corticoids is greater than when delivered via MDI; half the dose produces the same effect. Despite these data, there have been few studies comparing DPIs to MDIs in efficiency of salbutamol delivery.

METHOD

This was a prospective study involving 60 patients referred to the Pulmonary Function Laboratory at the *Pavilhão Pereira Filho of the Santa Casa de Misericórdia de Porto Alegre* (Rio Grande do Sul, Brazil) for the investigation of symptoms (cough, dyspnea, and wheezing) related to bronchial hyperresponsiveness.

Spirometry tests revealed a forced expiratory volume in one second/forced vital capacity ratio (FEV₁/FVC, Tiffeneau index) superior to 70% in all patients, and none of the patients were using inhaled bronchodilators or inhaled corticoids. Patients presented bronchospasm as a consequence of a bronchoprovocation test by means of methacholine administration. A protocol of inhaled methacholine administration via jet nebulizer for 2 minutes was adopted, according to guidelines established by the *Sociedade Brasileira de Pneumologia e Tisiologia* (SBPT, Brazilian Society of Pulmonology and Phthysiology)⁽⁷⁾. Administration of variable concentrations of methacholine resulted in a decrease of at least 20% in FEV₁ in relation to the initial values in all of the patients studied. After the induction of bronchoconstriction, the 60 patients were randomized into two groups of 30. In group 1 (MDI group) patients, 200 μ g of salbutamol

were administered by MDI (2 jets with a 50-mL aerochamber) immediately after bronchoprovocation according to the method recommended by the SBPT(1). Patients in group 2 (DPI group) received 200 µg of salbutamol (1 inhalation) by DPI (Pulvinal; Butovent®). Patients were asked to exhale completely and, while holding the device slightly inclined, inhale as deeply as possible, then hold their breath for at least 5 seconds. A physician from the Pulmonary Function Laboratory administered the bronchodilator, using the appropriate technique. A laboratory technician, blinded as to which device each patient was using, was responsible for spirometry, which was always performed in the morning. At one minute and five minutes after salbutamol administration, patients were submitted to spirometric tests for the determination of FEV₁.

The following demographics and variables were determined: gender, age, height, weight, dose level provoking a 20% drop in FEV₁ (DL₂₀), initial FEV₁, post-methacholine FEV₁, FEV₁ at one minute after bronchodilator administration and FEV₁ at five minutes after bronchodilator administration.

Pearson's chi-square test was used to compare proportions, whereas Student's *t*-test was used for the comparison between means. A 95% level of statistical significance was adopted. After data analysis, we evaluated the statistical power of comparisons and found values of approximately 90%, guaranteeing that the

sample used was sufficient for the objectives of the study.

The Ethics Research Committee of the *Complexo Hospitalar da Santa Casa de Misericórdia de Porto Alegre* approved this study.

RESULTS

Gender, age, weight, and DL₂₀ were similar in both the MDI group and the DPI group (Table 1).

Prior to the bronchoprovocation test, pulmonary function parameters were comparable between the groups. In the MDI and DPI groups, respectively, initial FEV₁ was 2.88 L and 2.9 L and FEV₁ after bronchoprovocation with methacholine was 2.03 L and 1.99 L (Table 2). In the MDI group, mean FEV₁ at one minute after salbutamol administration was 2.36 L, 16.2% greater than post-methacholine FEV₁, whereas the same parameter in the DPI group was 2.33 L, a mean increase of 17% - representing no statistically significant difference between the two groups (*p* = 0.89). Mean FEV₁ at five minutes after salbutamol administration was 2.48 L in the MDI group (22.2% increase over post-methacholine FEV₁) and 2.46 L in the DPI group (23.6% higher than post-methacholine FEV₁), demonstrating an almost absolute similarity between both groups (*p* = 0.8) (Figure 1).

TABLE 1
Characteristics of patients submitted to methacholine-induced bronchoconstriction

	MDI GROUP	DPI GROUP	<i>p</i>
Gender			
Male	5	6	0.739
Female	25	24	0.741
Age (years)	42.46 ± 18.91	47.63 ± 18.61	0.291
Height (cm)	162.36 ± 9.48	162.06 ± 8.49	0.900
Weight (kg)	65.46 ± 15.15	67.60 ± 11.78	0.545
DL ₂₀ (mg/dL)	1.30 ± 1.78	1.19 ± 1.42	0.793

*RESULTS EXPRESSED AS MEAN ± STANDARD DEVIATION; DL₂₀: DOSE LEVEL PROVOKING A 20% DROP IN FEV₁.

TABLE 2
Functional characteristics of patients submitted to methacholine-induced bronchoconstriction and variation after the use of the bronchodilator

	MDI GROUP	DPI GROUP	<i>p</i>
Initial FEV ₁ (L)	2.88	2.90	0.952
Post FEV ₁ (L)	2.03	1.99	0.868
FEV ₁ 1 MIN (L)	2.36	2.33	0.898
FEV ₁ 5 MIN (L)	2.48	2.46	0.930

Initial FEV₁: Forced expiratory volume in one second prior to methacholine-induced bronchoconstriction; Post FEV₁: FEV₁ after methacholine-induced bronchoconstriction; FEV₁ 1 MIN: FEV₁ at one minute after bronchodilator administration; FEV₁ 5 MIN: FEV₁ at five minutes after bronchodilator administration.

DISCUSSION

Our results indicate that, in patients submitted to methacholine-induced bronchoconstriction, there is virtually no difference between the MDI and DPI (Pulvinal) methods of salbutamol administration in the degree of post-salbutamol bronchodilation achieved. Bronchodilator response (measured by FEV₁) at one and five minutes after salbutamol administration was practically the same with the use of both devices. Both FEV₁ variation in liters and the percentage of response were very similar, indicating that the bronchodilator effect of salbutamol is comparable when administered by either device.

There have been very few international studies comparing the bronchodilator effect of MDIs to that of DPIs. Since the Pulvinal DPI is a new device, there are no studies similar to ours in the literature. The few studies published have made use of the Turbuhaler DPI.

The results of the present study were similar to those of previous studies in the literature evaluating other DPIs. Chapman et al.(6) designed a study involving 37 asthmatic patients who received salbutamol via Turbuhaler or MDI. Morning FEV₁ and peak expiratory flow (PEF) were measured for 2 weeks. The authors used a salbutamol dose of 200 µg for MDIs and 100 µg for DPIs and found no differences between the two devices in FEV₁ and PEF values, despite the lower salbutamol dose given via DPI. Another study involving 50 patients with moderate to severe reversible airway obstruction(8)

compared the bronchodilator effects of 200-µg salbutamol doses via DPI and via MDI. The bronchodilator response during and 6 hours after administration was similar in both cases. Mellén et al.(9), in a study involving 22 asthma patients, found the increase in FEV₁ after the administration of salbutamol to be similar whether the drug was delivered via MDI or via DPI. In the same study, neither levels of potassium and glucose nor heart rate presented significant differences, indicating that efficiency and safety were also similar between the two devices. In a study conducted by Bondesson et al.(10), similar results regarding efficiency and side-effect tolerability were found in 12 patients with moderate to severe asthma.

The similar or even superior efficiency of salbutamol administered via DPI when compared to MDI administration may be due to a greater deposition of the substance in the lower airways, causing higher bronchodilator activity in peripheral airways. It has been reported that 20% of the substance is deposited in the lungs and airways when delivered by DPI(11), considerably higher than the 7% to 10% reported for MDI delivery(12).

Although the present study evaluated bronchodilator response in patients submitted to methacholine-induced bronchoconstriction, the results may be extrapolated to asthmatic patients whose bronchoconstriction mechanism presents a bronchospastic component. Various studies have used this technique in the analysis of the bronchodilator efficiency of various

substances and various inhaler devices⁽¹³⁾. Since we observed that the degree of bronchodilation was the same whether the substance was delivered via DPI or via MDI, we can conclude that the use of DPI is an efficacious option for the reversal of bronchoconstriction in asthma attacks. In another study⁽¹⁴⁾, 86 patients with acute asthma presenting to an emergency room with a mean FEV₁ of 37% were randomized to receive salbutamol in similar doses via Turbuhaler or via MDI with a spacer. Electrocardiograms, FEV₁, PEF, serum potassium, heart rate, and arterial blood pressure (measured every 10 minutes for 85 minutes) were studied. There was no significant difference between the two methods of administration in degree of bronchodilation attained or number and severity of side effects.

In a similar study, in which 23 asthmatic patients were submitted to methacholine-induced bronchoconstriction, Wong et al.⁽¹⁵⁾ reported that the protective effect of salbutamol against bronchoconstriction was more pronounced when the drug was delivered via Turbuhaler than when delivered via MDI. In a study carried out by Mellén et al.⁽¹⁶⁾, 20 asthmatic patients with airway obstruction received salbutamol via MDI or via Turbuhaler. The authors found FEV₁ variation, as well as changes in serum potassium, heart rate, and arterial blood pressure, to be similar between the two devices.

Several authors have reported the difficulties that asthmatic patients have in using MDIs correctly^(17,18,19). In a recent study, Muniz et al.⁽⁵⁾ reported that up to 40% of patients and physicians handled MDIs incorrectly due to poor respiratory and mechanical coordination. The same study reported that only 12% of patients and physicians used DPIs incorrectly. Since DPIs are placed directly into the mouth, coordination of respiratory movements is more efficacious than when using MDIs, whose utilization requires notions of distance, motor coordination, and sufficient training in order to coordinate inhalation

with the actuation of the MDI. Asthmatic patients with severe obstruction, as well as the elderly, can usually inhale with sufficient force to use the Pulvinal or other DPIs. In a study involving 52 patients (some elderly) with severe asthma, inhalation rates of up to 20 L/min allowed variation in peak flow and FEV₁ that were considered satisfactory⁽²⁰⁾. Similar results were found in studies of Pulvinal DPI-delivered beclomethasone administered to asthmatic patients⁽²¹⁾.

The present study revealed that, in patients submitted to methacholine-induced bronchoconstriction, the improvement in functional efficiency, quantified through assessment of FEV₁ at one and five minutes after salbutamol administration, was similar whether the drug was delivered via MDI or via DPI. We can conclude that β_2 -agonists delivered by DPI (Pulvinal) present the same bronchodilator efficiency and speed of action as do those delivered by the more traditional MDI method. Due to their ease of use and efficacy, DPIs present a viable alternative for immediate relief of bronchoconstriction in asthmatic patients, and their selection may result in higher rates of patient adherence to treatment.

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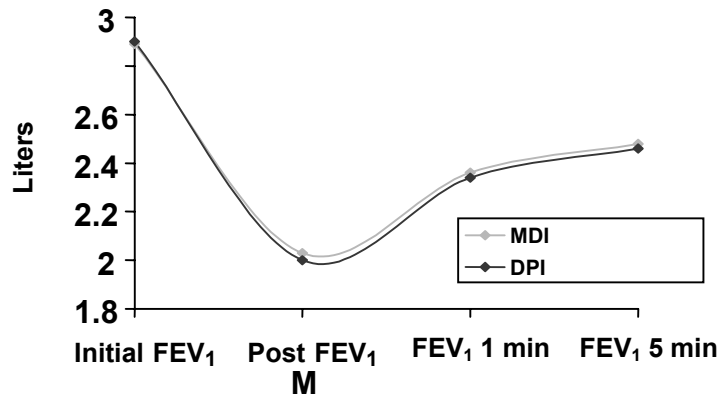


Figure 1: FEV₁ variation curve after methacholine-induced bronchoconstriction and bronchodilator response in both groups. Initial FEV₁: Forced expiratory volume in one second prior to methacholine-induced bronchoconstriction; Post FEV₁: FEV₁ after methacholine (M)-induced bronchoconstriction; FEV₁ 1 MIN: FEV₁ at one minute after bronchodilator administration; FEV₁ 5 MIN: FEV₁ at five minutes after bronchodilator administration; MDI: metered-dose inhaler, DPI: dry-powder inhaler.