The Protective Effect of Salbutamol Inhaled Using Different Devices on Methacholine Bronchoconstriction*

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Study objective: To determine the protective effect of salbutamol, 100 μg, inhaled by different devices (pressurized metered-dose inhaler [pMDI; Ventolin; GlaxoWellcome; Greenford, UK], pMDI + spacer [Volumatic; GlaxoWellcome], or breath-activated pMDI [Autohaler; 3M Pharmaceuticals; St. Paul, MN]) on bronchoconstriction induced by methacholine.

Design: Randomized, double-blind, cross-over, placebo-controlled study.

Patients: Eighteen subjects with stable, moderate asthma, asymptomatic, receiving regular treatment with salmeterol, 50 μg bid, and inhaled beclomethasone dipropionate, 250 μg bid, in the last 6 months, with high hyperreactivity to methacholine (baseline provocative dose of methacholine causing a 20% fall in FEV₁ [PD₂₀] geometric mean [GM], 0.071 mg). Subjects were classified into two groups: subjects with incorrect (n = 5) pMDI inhalation technique, and subjects with correct (n = 13) inhalation technique.

Methods and measurements: After cessation of therapy for 3 days, all subjects underwent four methacholine challenge tests, each test 1 week apart, each time 15 min after inhalation of salbutamol, 100 μg (via pMDI, pMDI + spacer, or Autohaler), or placebo. The protective effect on methacholine challenge test was evaluated as the change in the PD₂₀, and expressed in terms of doubling doses of methacholine in comparison with placebo treatment.

Results: The PD₂₀ was significantly higher after salbutamol inhalation than after placebo inhalation, but no significant difference was observed among the three different inhalation techniques. Only when salbutamol was inhaled via pMDI + spacer, PD₂₀ was slightly but not significantly higher (pMDI GM, 0.454 mg; pMDI + spacer GM, 0.559 mg; and Autohaler GM, 0.372 mg; not significant [NS]) than other inhalation techniques. Similar results (mean ±SEM) were obtained with doubling doses of methacholine (pMDI, 2 ± 0.47; pMDI + spacer, 3 ± 0.35; and Autohaler, 2.4 ± 0.40; NS). No significant difference was found among techniques when subjects with correct or incorrect inhalation technique were separately considered.

Conclusions: Our data show that the protective effect of salbutamol, 100 μg, on methacholine-induced bronchoconstriction is not affected by the different inhalation techniques, although inhalation via pMDI + spacer tends to improve the bronchoprotective ability of salbutamol. These data confirm the clinical efficacy of salbutamol, whatever the device, and the patient’s inhalation technique.

Key words: inhalation devices; methacholine challenge test; salbutamol

Abbreviations: PD₂₀ = provocative dose of methacholine inducing a 20% fall in FEV₁; pMDI = pressurized metered-dose inhaler

Delivering drugs directly into the airways via inhalation is generally preferred to systemic drug delivery in the management of chronic asthma.¹

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It is well known that inhalation devices and the quality of the inhalation technique influence the deposition of drug in the lung.² The degree of lung deposition studied by gamma scintigraphy or by specific pharmacokinetics ranges from 10% for pressurized metered-dose inhalers (pMDIs)³ to 26% for dry powder inhalers.⁴ The poor lung deposition obtained with a pMDI can be partially due to the fact that actuation of the pMDI and inspiration are not simultaneous. The use of extension reservoir devices (spacers)⁵ or of a breath-activated pMDI, such as the
Autohaler (3M Pharmaceuticals; St. Paul, MN) is often recommended in order to increase lung deposition. Despite this great difference in lung deposition, the efficacy of different devices, particularly in terms of acute bronchodilation induced by short-acting $\beta_2$-agonists, is not well defined. Several studies have shown a similar bronchodilation pattern after single or cumulative doses of terbutaline or salbutamol. However, Lofdahl et al demonstrated that salbutamol, 200 $\mu$g, given via the Turbuhaler (AstraZeneca; Lund, Sweden) induced a significantly better response than when given via pMDI, and studies have shown that the Turbuhaler delivers about twice as much the amount of drug to the lungs as the pMDI.

A method often used in the evaluation of the efficacy of inhaled drugs is the protective effect on methacholine or histamine-induced bronchoconstriction. The inhalation of a short-acting $\beta_2$-agonist increases the provocative dose of inhaled methacholine or histamine from 1.1 to 3.9 doubling doses. More recent studies have demonstrated that salbutamol increases the provocative dose of methacholine by 2.8 to 3.1 doubling doses.

In this study, we compared the protective effect of salbutamol, 100 $\mu$g, inhaled by different devices (pMDI [Ventolin; GlaxoWellcome; Greenford, UK], pMDI + spacer [Volumatic; GlaxoWellcome], and Autohaler) on methacholine-induced bronchoconstriction in a double-blind, cross-over, placebo-controlled study.

**Materials and Methods**

**Subjects**

We investigated 18 asthmatic subjects (10 male, 8 female; 11 nonsmokers, 7 ex-smokers; mean age, 40 ± 18 years) in a stable phase of the disease (Table 1). Asthma diagnosis was made according to international guidelines. All subjects had high baseline levels of airway reactivity to methacholine (provocative dose of methacholine causing a 20% fall in FEV$_1$ [PD$_{20}$] geometric mean, 0.071 mg). All subjects were receiving regular treatment with inhaled long-acting $\beta_2$-agonists (salmeterol, 50 $\mu$g bid) and inhaled corticosteroids (beclomethasone dipropionate, 500 $\mu$g bid). The treatment remained stable for 4 weeks before the study and during the study period, and was withdrawn 3 days before each methacholine challenge test. At the time of the present investigation, all subjects were classified as having moderate asthma.

**Study Protocol**

The study had a randomized, double-blind, cross-over, placebo-controlled design, comparing the effect of salbutamol inhaled by means of different devices on methacholine challenge test. All subjects underwent four methacholine challenge tests on 4 different days, each test 1 week apart, protected in randomized order by either placebo treatment or salbutamol, 100 $\mu$g (1 puff), inhaled 15 min before the challenge via pMDI alone, pMDI + spacer, or Autohaler. Since the study was double blind, the subjects inhaled one puff from each device, according to the scheme shown in Figure 1, before each methacholine challenge test. Two or all devices administered placebo before each methacholine challenge test (Fig 1). The pMDI was primed and

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*F = female; M = male; NO = nonsmoker; EX = ex-smoker.

**Figure 1.** Protocol schedule. The patients underwent drug sequences top, A; upper center, B; lower center, C; and bottom, D before each methacholine challenge test. The order of the sequences was double blind and randomized.
shaken before each inhalation. All patients regularly took their therapy throughout the whole study, except for the 3 days preceding each methacholine challenge test. Salbutamol use was allowed as rescue medication up to 12 h before each methacholine challenge test, and only in 4 of 18 subjects needed it. The technical personnel in charge of the pulmonary function tests was not aware of the patient’s treatment.

Assessment of Inhalation Technique

The pMDI inhalation technique of the enrolled subjects was evaluated by three physicians. The inhalation technique was divided in four steps: (1) the aim of the spray; (2) coordination of inhalation and actuation; (3) inspiratory time; and (4) apnea after inhalation. Each step could be rated as acceptable or nonacceptable. The inhalation technique was recorded as incorrect when only one step was judged as nonacceptable by at least two physicians.

Methacholine Challenge Test

Methacholine was delivered by a jet nebulizer (model 646; DeVilbiss Health Care; Somerset, PA) using the procedure described elsewhere. Briefly, phosphate-buffered saline solution was inhaled first, followed every 2 min by methacholine inhalation from 0.04 to 3.2 mg of cumulative doses of methacholine in different steps. FEV₁ was measured 2 min after each step. The test was stopped when FEV₁ fell ≥ 20% below the postdiluent value, and PD₂₀ was computed.

Statistical Analysis

FEV₁ is expressed as mean ± SD; FEV₁ (percent predicted) is expressed as median (range). PD₂₀ is expressed as geometric mean (in milligrams). The change in PD₂₀ between the tests was calculated (in doubling doses) by the following formula: $\Delta \log PD_{20}/\log 2$ (that is, 0.5). Doubling doses of inhaled methacholine were expressed as mean ± SEM. To compare groups of observations, the Friedman test and Wilcoxon test were used.

Results

The baseline value of FEV₁ before each methacholine challenge test was not significantly different among the four groups, both as absolute value and as percent of the predicted value (Table 2). A single dose of salbutamol induced a mild bronchodilation with all devices that was significantly higher, compared to bronchodilation obtained after placebo. PD₂₀ was significantly lower after placebo than after salbutamol treatment, but no difference was observed among pMDI, pMDI + spacer, and Autohaler, although reactivity to methacholine tended to be lower after salbutamol administered by pMDI + spacer. The increasing doubling doses of methacholine, obtained by the different devices with respect to placebo, were slightly but not significantly higher in the pMDI + spacer group.

When subjects were classified on the basis of pMDI inhalation technique, 13 subjects showed a correct inhalation technique and 5 subjects showed an incorrect inhalation technique. No significant difference between devices was found when subjects with a correct pMDI inhalation technique and with an incorrect pMDI inhalation technique were separately considered (Fig 2). However, in subjects with an incorrect inhalation technique, PD₂₀ tended to be higher after salbutamol administered via pMDI + spacer (Fig 2). In both groups, the reactivity to methacholine was lower after salbutamol.

![Figure 2. LogPD₂₀ (LogPD₂₀FEV₁ Methacholine: mean ± SD) during methacholine challenge test protected by placebo and salbutamol inhaled by pMDI, pMDI + spacer, and Autohaler, in subjects with correct pMDI inhalation technique (n = 13; black bars) and in subjects with incorrect pMDI inhalation technique (n = 5; dashed bars). * = p < 0.05 between placebo and other groups by Friedman test.](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21945/ on 06/26/2017)
than after placebo treatment. Similar results were found with increasing methacholine doubling doses: correct inhalation group (n = 13; mean ± SEM) for pMDI, 2.9 ± 0.60; pMDI + spacer, 3.0 ± 0.46; and Autohaler, 2.5 ± 0.57 (not significant); incorrect inhalation group (n = 5; mean ± SEM) for pMDI, 2.0 ± 0.68; pMDI + spacer, 2.8 ± 0.56; and Autohaler, 2.1 ± 0.37 (not significant).

**DISCUSSION**

Our data show that the bronchoprotective effect of salbutamol, 100 μg, on methacholine challenge is not affected by the different inhalation technique, although the inhalation via pMDI + spacer tends to improve the salbutamol protection on methacholine challenge test. The correct pMDI inhalation technique does not significantly influence the salbutamol protective effect.

A previous, well-designed comparative study demonstrated that salbutamol, 200 μg, given via Turbuhaler showed a significantly better response than when given via pMDI, but no difference was observed among salbutamol, 50 μg and 100 μg, via Turbuhaler and salbutamol, 200 μg, via pMDI. In another study, it was demonstrated that half the dose given via Turbuhaler will produce the same effect as the full dose given via pMDI. However, these studies evaluated the bronchodilatory effect of salbutamol administered at two different dose levels. To our knowledge, no studies have compared the different bronchoprotective effect of a single therapeutic dose of salbutamol inhaled by different devices on methacholine challenge test. In our study, we evaluated the effect of only one dose of drug, and even if the design is inadequate to detect the drug potency or the dose at which salbutamol can have different functional effect. It can, however, show whether the devices and the quality of the inhalation technique affect salbutamol efficacy at the usual therapeutic doses. pMDI, pMDI + spacer, and Autohaler represent the most common devices for inhalation of salbutamol that are used by asthmatics with different degree of airways obstruction. Our patients are representative of the majority of patients who usually use medications via inhalation; these subjects are usually well trained in the use of inhaler devices, and they often use salbutamol as rescue medication.

One actuation of salbutamol via pMDI, pMDI + spacer, or Autohaler had similar bronchoprotective effect on methacholine challenge test. This evidence is no different from the results of previous studies evaluating the bronchodilation activity of a single dose of salbutamol via different devices. In particular, salbutamol, 200 μg, given either via Autohaler or via pMDI determined a similar increase in FEV₁.

However, the effect of inhalation systems depends on the way the patient uses them. Particularly, the coordination of actuation and inhalation, and the inhalation modes are the critical points of a good inhalation technique. The real efficacy of the spacer in improving the inhalation technique is still debated, particularly when considering the volume of the different spacers or the deposition of the drug onto the spacer wall caused by electrostatic spacer properties. Large spacers are compatible with any pMDI and seem to be the best way to minimize the effect of an incorrect inhalation technique. In our experience, the bronchoprotective effect of salbutamol was no different in patients who use a large spacer or not, but the patients with an incorrect inhalation technique tended to have lower levels of airways hyperreactivity after salbutamol inhalation by pMDI + spacer than after salbutamol administered by other devices.

The therapeutic dose of salbutamol inhaled as a rescue medication shows a similar clinical effect on bronchoconstriction stimuli even when administered by different inhalation systems. The way the patient uses the systems only partially affects the bronchoprotective effect of salbutamol on methacholine bronchoconstriction, and this can be partially improved by use of a spacer. This evidence permits the use of salbutamol as rescue medication, using any device and with any inhalation technique.

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**REFERENCES**

24 Barry PW, O’Callaghan C. Multiple actuations of salbutamol MDI into spacer devices reduce the amount of drug recovered in the respirable range. Eur Respir J 1994; 84:1707–1709
25 Chege JK, Chrystyn H. Volumatic usage: some generic salbutamol metered dose inhalers can be used. Thorax 1994; 49:1162–1163