

The Spacehaler[™] for delivery of salbutamol: a comparison with the standard metered-dose inhaler plus Volumatic[™] spacer device

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The Spacehaler[™] is a new, compact, pressurized aerosol device that uses the same canister as a conventional metered-dose inhaler (MDI). Its design, however, reduces the velocity of the aerosol cloud that emerges from the inhaler, thereby reducing the amount of the non-respirable fraction of the drug delivered to the patient. Large volume spacers achieve a similar effect, but they are bulky and therefore inconvenient to use and carry around. This study compared the bronchodilator effect of 200 μ g salbutamol delivered by the Spacehaler[™] to that of an MDI used with a Volumatic[™] spacer (MDI plus spacer) in patients with reversible obstructive airways disease.

Twenty-five patients with asthma, having a forced expiratory volume in 1 s (FEV₁) between 50 and 90% predicted and a reversibility of $\geq 15\%$ to 200 μ g salbutamol given by the conventional (standard) MDI entered the study. On two separate study days, they inhaled 200 μ g salbutamol either via the Spacehaler[™] or the MDI plus spacer. To maintain blinding, they received placebo on both study days via the alternate device. Their FEV₁, forced vital capacity (FVC) and peak expiratory flow (PEF) were measured before and at regular intervals for 6 h after inhalation. Assessment of equivalence between the two devices was based on whether the 90% confidence interval for the difference between the weighted mean FEV₁ was within ± 0.25 l. Patient preference was assessed by a questionnaire at the end of the second study day.

Twenty-four patients completed the study. Both devices produced a significant improvement in FEV₁ ($P < 0.02$). The upper and lower 90% confidence limits for the difference in weighted mean FEV₁ between the devices was ± 0.041 , and the 99% confidence limits were $+0.061$ and -0.071 . The weighted means for FVC and PEF, and the duration of effect and peak responses for FEV₁, FVC and PEF also showed no difference between the two devices. Patients found no difficulty in using the Spacehaler[™], and 20 out of 24 patients (83.3%) preferred it to the MDI plus spacer.

The bronchodilator effect of 200 μ g salbutamol administered by a Spacehaler[™] was equivalent to that produced by an MDI plus spacer in this group of patients with reversible airways obstruction. The majority of patients preferred it to a large volume spacer.

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Introduction

The pressurized metered-dose inhaler (MDI) is the most common inhaler device used for the

treatment of patients with reversible obstructive airways disease, and has been available for more than 30 yr. It is inexpensive, reliable and efficient (1), and delivers multiple reproducible doses of drug. However, the aerosol of drug emitted from the MDI contains a large proportion of non-respirable particles greater than 5 μ m in diameter (2). The high velocity of the aerosol particles (30 m s⁻¹) results in most of these impacting in

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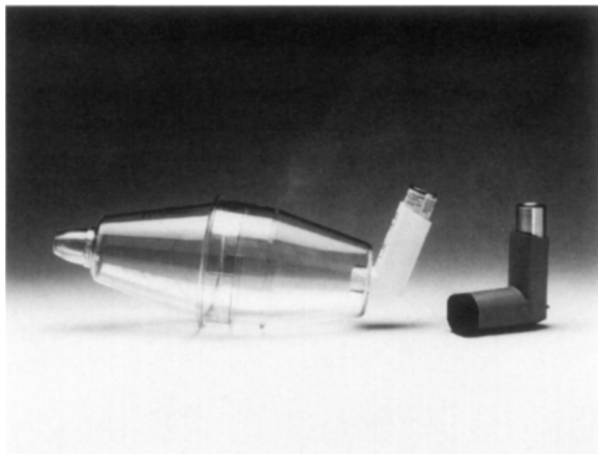


PLATE 1. The Spacehaler[™] device (right) and the standard MDI plus Volumatic[™] spacer (left), to show relative sizes.

the oropharynx, where up to 80% of the drug delivered may be deposited (3). The high velocity may also produce an unwanted 'cold-Freon effect', causing some patients to stop inspiration with the release of aerosol into the mouth (4).

Large volume spacer devices reduce oropharyngeal deposition and the 'cold-Freon effect' (5). Spacers are of particular value in the treatment of patients requiring high-dose inhaled corticosteroids and patients who are prone to develop candidiasis with inhaled steroids (6).

A variety of spacer devices are available for use with the standard MDI. The size of many of these devices, however, makes them inconvenient to carry for use outside the home. A smaller inhalation device with a deposition profile similar to that of a spacer which produces a slow-velocity spray, would be a useful alternative for inhaled drug therapy for patients unable to use the standard MDI because of the 'cold-Freon' effect, and also for those patients using large volume spacers for inhaled corticosteroid therapy. Although dry powder inhalers may be appropriate for many patients, they are relatively expensive and do not reduce oropharyngeal deposition.

The Spacehaler[™] (previously called the Gentlehaler[™]) has been developed to address this requirement (7). The key benefits of the Spacehaler[™] are: (i) that it slows down the velocity of the delivered dose from 30 to 2 m s⁻¹ (8); and (ii) that it retains within the device the majority of the non-respirable fraction of the

emitted dose, thereby reducing oropharyngeal deposition (8).

The present study compared the bronchodilator effect of 200 µg salbutamol administered either via a Spacehaler[™] or standard MDI used in conjunction with a Volumatic[™] spacer device (MDI plus spacer) in patients with reversible obstructive airways disease. The dose of 200 µg of salbutamol was chosen since this is the most commonly recommended dose in clinical practice. The ease of use, patient preference, the effects on heart rate and blood pressure and the occurrence of adverse events were also assessed.

Methods

SPACEHALER[™] DEVICE

The Spacehaler[™] (Evans Medical Ltd, Leatherhead, U.K.) is a compact, low-velocity, pressurized aerosol device which is 7.5 cm long compared to the standard MDI plus Volumatic[™] spacer which is 26 cm long (Plate 1). It uses the same canister as a conventional MDI. Its design incorporates a vortex chamber immediately upstream of the nozzle, together with a narrow air inlet in the rear and a bell-shaped internal surface in the mouthpiece. The overall effect is to reduce the velocity of the spray and to retain most of the non-respirable particles within the actuator. Oropharyngeal deposition is therefore reduced (8).

PATIENTS

Twenty-five patients (13 males) with a documented history of stable asthma entered the study (mean age 46 years; age range 22–70). There were 10 non-smokers, 11 ex-smokers and four current smokers. They had a forced expiratory volume in 1 s (FEV₁) ≥ 50% but ≤ 90% of that predicted by the European Community for Coal and Steel (ECCS) formulae; mean FEV₁ 2.08 l (SD 0.62 l, range 1.04–3.34 l). All showed an increase in FEV₁ of ≥ 15% after inhalation of 200 µg salbutamol using a standard MDI (without spacer). Patients were permitted to continue inhaled corticosteroids, sodium cromoglycate and nedocromil sodium during the study, provided that the dose was regular and remained

constant. Oral corticosteroids and theophyllines were not allowed; anti-cholinergics and oral and long-acting β_2 agonists were discontinued for 24 h, and short-acting β_2 agonists were discontinued for 10 h prior to study visits.

STUDY DESIGN

This was a single-centre, randomized, double-blind, double-dummy, crossover study. Patients attended the clinic on three occasions. At the first visit, eligibility and reversibility criteria were assessed. Patients who satisfied the entry criteria were randomized sequentially to study treatment according to a computer-generated randomization code, and attended on two further study days.

At these visits, patients received two puffs of salbutamol from a pressurized aerosol canister ($100 \mu\text{g puff}^{-1}$) with one of the inhaler devices, and two puffs of placebo with the other inhaler device. One of the inhaler devices was the Spacehaler[™] and the other was a standard MDI attached to a Volumatic[™] spacer (Allen & Hanbury Ltd, Uxbridge, Middlesex, U.K.). Before use, each spacer was washed with warm soapy water and allowed to air dry overnight, to reduce the possibility of electrostatic attraction of drug particles to the spacer (9). Before inhalation, the devices were primed by firing the Spacehaler[™] or the MDI twice into a plastic bag. The salbutamol and the placebo aerosol canisters were manufactured by Baker-Norton, Harlow, Essex, U.K. The device containing the active drug and the order of use of the devices were randomized in blocks of four. Lung function measurements [FEV₁, forced vital capacity (FVC) and peak expiratory flow (PEF)], pulse and blood pressure were measured before and at 15, 30, 60, 120, 180, 240, 300 and 360 min after treatment. At the third visit, the baseline FEV₁ was required to be within $\pm 15\%$ of the value recorded at the second visit, so that baseline FEV₁ on both treatment days was comparable. All lung functions were measured using three factory-calibrated Microlab 3000 electronic turbine spirometers (Micro Medical Ltd, Rochester, Kent, U.K.). The calibrations were checked daily throughout the study to ensure that there was no drift. Any one patient used the same spirometer throughout the study.

Approval for the study was obtained from the Research Ethics Committee of East Berkshire Health Authority.

EVALUATION OF DEVICE HANDLING

At the first visit, patients were given time to read the instructions for using the Spacehaler[™] and the MDI plus spacer, after which their ability to use the devices was assessed. The number of attempts required to assemble each device and inhale correctly was recorded. Further instruction was given if needed, and the need for this was recorded. At the end of the study, patients' evaluation of the ease of use of the two inhaler devices and their personal preference were assessed by a questionnaire that investigated previous inhaler experience, features of the study devices and relative convenience, portability, comfort and co-ordination.

STATISTICS

Assessment of equivalence between the two devices was based on the null hypothesis that there is a difference, and whether the 90% confidence interval for the difference between the weighted mean FEV₁ was within ± 0.25 l (10–12). A sample size of 24 patients was required to give 90% power to detect no difference between treatments (10) assuming a within-patient standard deviation of 0.25 l. Weighted mean FEV₁ was calculated by dividing the area under the response time curve by time. Weighted means were also compared for FVC and PEF, and peak observed values, time to onset of effect and duration of action were compared for FEV₁, FVC and PEF. Onset of action was identified by the time point at which the test parameter increased by 15% or more over the baseline value. The duration of action was the total time the test parameter stayed above 15%. SAS version 6.08 (SAS Institute Inc., Cary, NC, U.S.A.) was used for the statistical procedures. Appropriate parametric (ANOVA, paired *t*-test) and non-parametric (Wilcoxon rank sum test, Kruskal-Wallis test, survival analysis) procedures were used, taking into consideration the distribution and censoring of data. For all statistical tests, a significance level of 5% was used. All tests were two-sided.

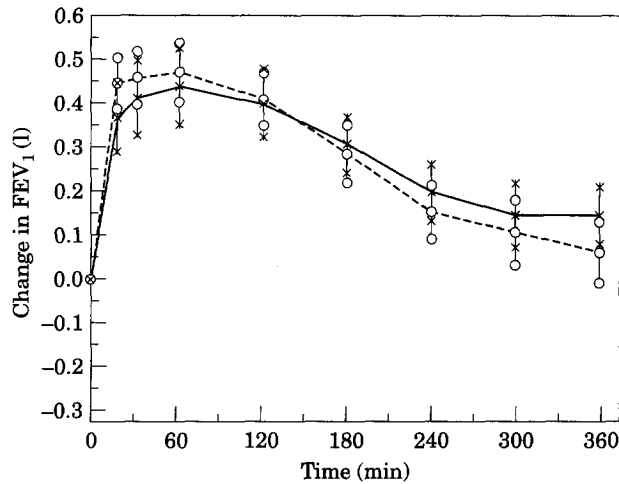


FIG. 1. Change in levels of FEV₁ during the active phase of the study period. ×, Spacehaler[®]; ○, metered-dose inhaler plus Volumatic[®] spacer.

Results

Of the 25 patients who entered the study, 24 completed both study periods. One patient withdraw because of family bereavement. Figure 1 shows the mean changes in FEV₁ (± 2 SEM) from baseline to each time point up to 360 min (6 h). The weighted change in mean FEV₁ from baseline was 0.28 l (SD 0.18 l) for the Spacehaler[®] and 0.27 l (SD 0.16 l) for the MDI plus spacer. The adjusted mean ($n=24$) for weighted mean FEV₁ was 2.38 l for the Spacehaler[®] and 2.38 l for the MDI plus spacer device. There was no significant difference between the two estimated population means ($P=0.87$; 90% confidence limits, $-0.043, 0.039$; 99% confidence limits, $-0.066, 0.062$). Individual patient data is shown in Fig. 2.

Multifactor ANOVA showed no difference between the two devices with respect to weighted mean FEV₁. There was no effect due to period or the order of usage of the devices. The effect for patients was significant ($P=0.0001$), which was not unexpected due to the natural variation of FEV₁ between patients.

The 90% upper and lower confidence limits for the difference between the two devices with respect to weighted mean FEV₁ were -0.043 and 0.039 . The 90% confidence interval was thus entirely contained within the equivalence interval of ± 0.25 l, and demonstrated that the two devices were equivalent. The 99% confidence

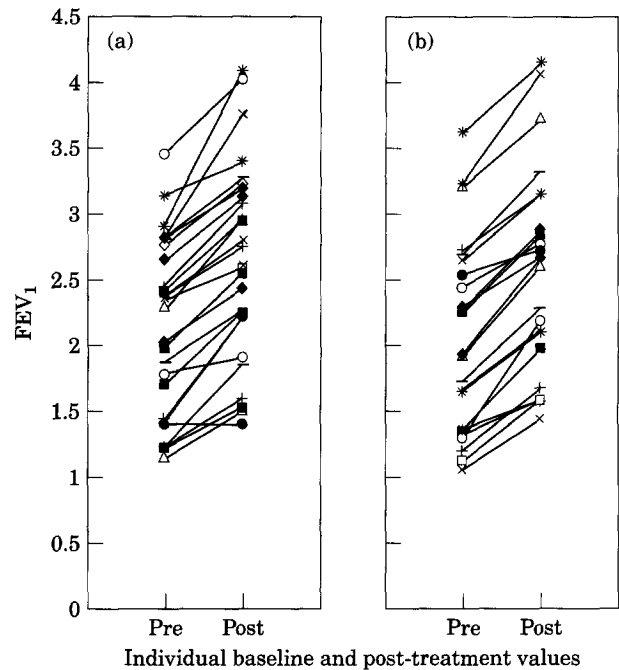


FIG. 2. Individual baseline and post-treatment values. (a) Spacehaler[®], (b) metered-dose inhaler plus Volumatic[®] spacer.

limits ($-0.066, 0.062$) were also well within the equivalence interval.

There was no difference between the two devices for the weighted means for FVC and PEF and peak values, time of onset and duration of effect as assessed by FEV₁, FVC and PEF. FEV₁ improved by an average of 0.49 l ($n=25$, SEM 0.05) with the Spacehaler[®] and 0.52 l ($n=24$, SEM 0.02) with the MDI plus spacer. These changes in FEV₁ were significant compared to the baseline values ($P=0.01$ for the Spacehaler[®], $P=0.005$ for the MDI plus spacer).

All patients had previously used an inhaler device of some kind. Twenty-three of 24 patients for whom this information was recorded had used an MDI previously. Fifty-eight per cent of these patients were able to use the Spacehaler[®] as per written instructions at the first attempt. The corresponding figure for the MDI plus spacer was 66%. The rest needed additional tuition once for both devices. There was no significant difference between the two devices as regards the ease of use.

The relative preferences and opinions of the patients with regard to the two devices, as expressed in the completed patient

TABLE 1. Numbers and percentages of patients expressing preferences for the Spacehaler[™] or the standard metered-dose inhaler (MDI) plus Volumatic[™] spacer device in response to questions on the patient questionnaire

	Number (%) of patients			
	Spacehaler [™]	MDI+spacer	Neither device	Both devices equal
Preferred device	20 (83.3)	3 (12.5)	1 (4.7)	0
More convenient to use	20 (83.3)	2 (8.3)	2 (8.3)	0
More comfortable to use	18 (81.8)	1 (4.6)	3 (13.6)	0
Easier to co-ordinate (patient perception)*	16 (73.9)*	1 (4.6)*	3 (13.6)*	2 (9.1)*
More portable	20 (83.3)	2 (8.3)	2 (8.3)	0

*For the purposes of this study, patients were required to demonstrate the ability to co-ordinate inspiration with dose release for both devices.

questionnaires, are shown in Table 1. The Spacehaler[™] was the preferred device, and the majority of patients thought it was more convenient and comfortable to use, easier to co-ordinate and more portable than the MDI plus spacer device. When asked if they would be happy if prescribed the Spacehaler[™], 21 of 24 patients (87.5%) said 'yes'.

Discussion

This study shows that the bronchodilator effect achieved by 200 µg of salbutamol using the Spacehaler[™] is identical to that achieved using a standard MDI with a Volumatic[™] spacer. The confidence limits for the difference show that one can be 99% certain that the difference in the weighted mean FEV₁ between the two devices is no more than 0.071 l. Analyses of other variables also showed no difference between the devices.

These findings confirm and extend the observations of two previous studies with a low-velocity pressurized aerosol inhaler. Newman and Clarke (8) found that the FEV₁, FVC, PEF and maximum mid-expiratory flow rate showed similar increases with 100 µg of salbutamol delivered by a Gentlehaler[™] and a MDI used correctly. Chipps *et al.* (7) also found no difference in various lung functions after administration of three puffs of Proventil[™] (equivalent to 300 µg of salbutamol) either by a Gentlehaler[™] or an MDI used with an Aerochamber[™]. Further studies are required to

determine whether the Spacehaler[™] and MDI plus a large volume spacer are equally effective in achieving bronchodilation at lower dose levels of salbutamol, although the lowest available dose is 50 µg. Since the dose response for salbutamol tends to be flat above 200 µg, it is unlikely that higher dose studies would provide any useful information. Future studies to develop non-chlorofluorocarbon (hydrofluoroalkane) formulations will also be required.

Data recorded on device handling showed that around 60% of patients were able to use both inhalation devices correctly after reading the instruction leaflet. The rest of the patients needed additional tuition only once for both devices. There was no significant difference in the abilities of the patients to learn to use either device. At the end of the study, the majority of patients (more than 80%) preferred the Spacehaler[™], and most patients found it to be more portable, easier to co-ordinate, and more comfortable and convenient to use than the MDI plus spacer device. Only three patients preferred the Volumatic[™] Spacer plus MDI. Two of these were over 50 years of age, while 10 of the 20 patients who preferred the Spacehaler[™] were over 50 years of age. There was, therefore, no age-related bias in patient preference. In the study by Chipps *et al.* (7), the majority of patients (22 of 30, 73%) also preferred the Gentlehaler[™] to the standard MDI plus Aerochamber[™]. The Spacehaler[™] may, therefore, be a useful alternative to the standard

MDI plus spacer in appropriate patients, especially in cases where a reduction in oropharyngeal deposition and/or 'cold-Freon effect' is required.

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