Effect of multiple actuations, delayed inhalation and antistatic treatment on the lung bioavailability of salbutamol via a spacer device

D J Clark, B J Lipworth

Abstract

***Background* – The aim of this study was to extend previous in vitro observations regarding the effects of multiple actuations of aerosols into spacer devices, delayed inhalation, and antistatic treatment of spacer devices on the amount of drug delivered for inhalation. An in vivo study of lung bioavailability of salbutamol from a large volume (Volumatic) spacer was conducted.**

***Methods* – Ten healthy volunteers of mean age 20.5 years with a mean forced expiratory volume in one second of 112.1% predicted were studied in a randomised single blind (investigator blind) crossover study. 1200 µg of salbutamol was given with mouth rinsing (100 µg/puff) on four study days: single puffs via spacer, multiple puffs via spacer (3 × 4 puffs), single puffs with 20 second delay before inhalation via spacer, and single puffs via an antistatic treated spacer. All spacers, including those treated with antistatic, were prewashed prior to each study day. Measurements of lung bioavailability were made at five, 10, and 20 minutes after inhalation to determine peak (Cmax) and average (Cav) plasma salbutamol levels. Systemic β_2 responses including finger tremor, heart rate, and plasma potassium levels were also evaluated.**

***Results* – Single puffs from the spacer produced higher plasma salbutamol levels and greater systemic β_2 responses than either multiple puffs or single puffs with delayed inhalation for a 1200 µg dose. For Cmax this amounted to a 1.93-fold (95% CI 1.68 to 2.19) greater lung bioavailability for single puffs than for multiple puffs and a 1.80-fold (95% CI 1.59 to 2.00) greater lung bioavailability for single puffs than for single puffs with a 20 second delay. Comparison of the normal and antistatic treated spacers (both prewashed) revealed differences for Cmax with levels 1.23-fold (95% CI 1.04 to 1.41) greater for the normal spacer.**

***Conclusions* – Delayed inhalation from a Volumatic spacer and the use of multiple puffs results in a considerable decrease in the delivery of salbutamol to the lungs with an approximate twofold reduction in lung bioavailability. Washing a Volumatic spacer is as effective as an antistatic lining in reducing the effects of static charge on salbutamol delivery in vivo.**

(*Thorax* 1996;51:981–984)

Keywords: spacer, lung bioavailability, salbutamol, antistatic treatment, delayed inhalation, multiple actuations.

Department of Clinical Pharmacology, Ninewells Hospital and Medical School, University of Dundee, Dundee DD1 9SY, UK
D J Clark
B J Lipworth

Correspondence to:
Dr B J Lipworth.

Received 5 October 1995
Returned to authors
22 December 1995
Revised version received
15 April 1996
Accepted for publication
18 April 1996

Spacer devices are used to reduce the need for coordination and to increase drug deposition when inhaling drugs into the respiratory tract in the management of asthma.[1] They are also beneficial in reducing the local and systemic side effects of inhaled steroids.[2 3] They are particularly useful in childhood asthma and the addition of a face mask allows them to be used for preschool children as an alternative to nebulisers.[4]

A common concern amongst medical practitioners and parents of asthmatic children is that of the technique of using spacer devices which will reliably deliver inhaled medications in both normal use and in an acute asthma attack. For example, the parents of preschool children will often actuate a drug into a spacer device for the child and there may be a significant delay before the child then inhales from this. In vitro studies using the multistage liquid impinger model indicate that this delayed inhalation may significantly reduce the dose of drug delivered.[5–7] The current British Thoracic Society guidelines recommend the administration of multiple actuations of β_2 agonist from a spacer to patients as an alternative to a nebuliser,[8] such as in the case of a general practitioner called to see a patient with an asthma attack. Again, in vitro work suggests that the dose of inhaled drug may be much lower than anticipated with the use of multiple rather than single puffs.[5–7 9]

Another possible variable affecting lung bioavailability of medications from spacer devices is the degree of static charge of the spacer. Aerosol particles from a metered dose inhaler (MDI) are highly charged and therefore the higher the static charge on the walls of the spacer, the more likely it is that the drug will be deposited there and be unavailable for inhalation.[5 7]

The aim of this study was to examine the in vivo effects of these three variables on salbutamol lung bioavailability and associated systemic β_2 responses as follows: (1) single versus multiple puffs; (2) 20 second delay versus immediate inhalation; (3) antistatic treated spacer versus normal washed spacer.

Methods

Ten healthy male volunteers of mean (SE) age 20.5 (0.3) years with a forced expiratory volume in one second (FEV_1) of 112.1 (2.8)% predicted were studied in a randomised single blind (investigator blind) crossover study. All gave written informed consent and the study was approved by the Tayside medical ethics committee. Physical examination, biochemical and haematological parameters, and 12-lead electrocardiographic examination were normal before the start of the study. Single doses of 1200 μg salbutamol (Ventolin MDI, Allen and Hanburys, Uxbridge, Middlesex, UK) were given on four study days each separated by at least three days: (1) single puffs with Volumatic spacer (Allen and Hanburys, Uxbridge, Middlesex, UK); (2) multiple puffs (3 × 4 puffs) with Volumatic spacer; (3) single puffs with a 20 second delay before inhalation with Volumatic spacer; (4) single puffs with an antistatic treated Volumatic spacer. Each total dose of 1200 μg was given over the same time period of six minutes with mouth rinsing after every inhalation from the Volumatic spacer.

After the screening visit all subjects attended the laboratory on four separate days. They remained supine throughout the study period except when inhaling the salbutamol. A cannula was inserted into an antecubital vein and kept patent by bolus injections of heparinised saline. After 20 minutes rest baseline measurements of finger tremor (TR; log units), heart rate (HR; beats/min), and plasma potassium (K; mmol/l) were made. Subjects then inhaled the salbutamol over six minutes. Blood was taken for measurement of plasma salbutamol levels (ng/ml) at five, 10, and 20 minutes after inhalation of the last puff. Plasma potassium levels, heart rate, and tremor measurements were repeated 20 minutes after inhalation of the last puff in order to evaluate peak responses.

Six new Volumatic spacers were used in the study. Two were given a wash resistant antistatic coating of polyurethane dispersion (Static Safe Environments Ltd, Birmingham, UK). All of the Volumatic spacers, including those treated with antistatic, were washed before the start of the study. After every use on each study day the spacers were washed in warm water and left to drip dry. In this respect it was thought to be more clinically relevant to compare a washed antistatic spacer with a washed normal spacer than using a new spacer on each study day, as this more closely reflects the situation of a patient using a spacer device for regular inhaled therapy.

MEASUREMENTS

Finger tremor was measured by a previously validated method with an accelerometer transducer (Entran, Ealing, UK).[10] Four recordings were taken and the results stored on computer disc. Tremor power (>2 Hz) was calculated by spectral analysis using computer-assisted autovariance. The mean of the three lowest consistent readings was recorded and used in analysis.

All blood samples were measured in batches at the end of the study and assayed in duplicate. Plasma potassium levels were measured by flame photometry using an IL943 analyser (Instrumentation Laboratory Ltd, Warrington, UK). The intra-assay and inter-assay values for analytical imprecision were 0.41% and 1.04%, respectively.

Plasma salbutamol levels were assayed by high performance liquid chromatography (HPLC) with solid phase extraction and fluorescence detection as previously described.[11] The analytical imprecision for plasma salbutamol was 3.9% (intra-assay) and 4.1% (inter-assay) at 4 ng/ml, and 11.8% (intra-assay) and 12.6% (inter-assay) at 2 ng/ml.

STATISTICAL ANALYSIS

All responses were calculated as a change from baseline, with the tremor data being log transformed as these data were not normally distributed. Data were then analysed using a Statgraphics Software package (STSC Software Publishing Group, Rockville, USA). For all parameters comparisons were made by multifactorial analysis of variance (MANOVA) followed by Bonferroni's multiple range testing using subjects, time period, and treatments as within factors for the analysis. A probability value of $p<0.05$ (two tailed) was considered as being of significance. Ratios (and 95% CI) between treatments were also calculated from plasma salbutamol values for peak (Cmax) and average (Cav) levels where a significant difference was identified between two treatments. Values are given in the text as means and 95% CI for difference.

Results

The results showed that inhalation of single puffs produced significantly higher plasma salbutamol levels and systemic effects than salbutamol taken either as multiple puffs or with delayed inhalation for a 1200 μg dose (table 1). Plasma

Table 1 Mean plasma salbutamol levels and systemic β_2 responses

	Single puffs	*Multiple puffs*	*Single puffs with delayed inhalation*	*Antistatic treated spacer*
Cmax (ng/ml)	5.11	2.75*** (1.67 to 3.05)	2.92*** (1.50 to 2.88)	4.37** (0.27 to 1.21)
Cav (ng/ml)	4.49	2.54*** (1.24 to 2.66)	2.54*** (1.24 to 2.66)	3.95
Tremor (log units)	0.58	0.20*** (0.12 to 0.64)	0.30* (0.02 to 0.54)	0.47
Heart rate (beats/min)	13.5	6.0*** (1.87 to 13.13)	9.2* (−0.51 to 9.12)	14.3
Potassium (mmol/l)	0.57	0.31* (0.01 to 0.51)	0.44	0.52

95% confidence intervals are given where there is a significant difference between single puffs and any of the other treatments.
* $p<0.05$; ** $p<0.01$; *** $p<0.001$.

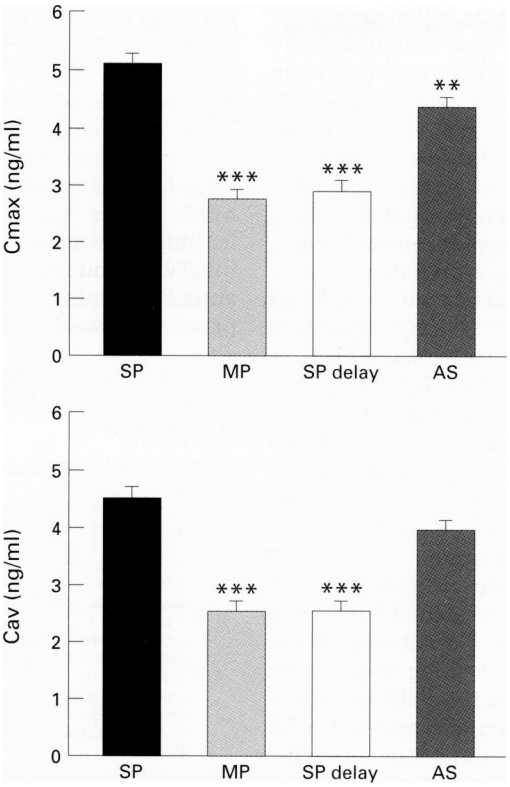

*Figure 1 Mean (SE) plasma salbutamol levels for peak (Cmax) and average (Cav) concentration with single dose of 1200 µg salbutamol given as single puffs with spacer (SP), multiple puffs with spacer (MP), single puffs with 20 second delay before inhalation from spacer (SP delay), and single puffs with an antistatic treated spacer (AS). Asterisks denote a significant difference between SP and any of the other inhalation sequences (**p<0.01, ***p<0.001).*

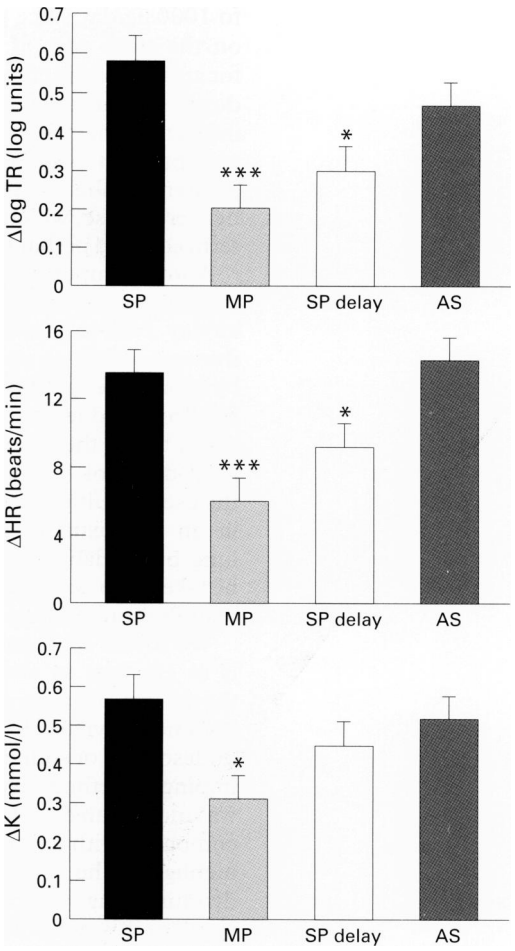

*Figure 3 Mean (SE) changes in tremor, plasma potassium levels, and heart rate with single dose of 1200 µg salbutamol given as single puffs with spacer (SP), multiple puffs with spacer (MP), single puffs with 20 second delay before inhalation from spacer (SP delay), and single puffs with an antistatic treated spacer (AS). Asterisks denote a significant difference between SP and any of the other inhalation sequences (*p<0.05, **p<0.01, ***p<0.001).*

salbutamol levels are shown in figs 1 and 2, and the systemic β_2 responses in fig 3.

The ratio between single and multiple puffs for Cmax was 1.93-fold (95% CI 1.68 to 2.19). Single puffs produced significantly higher levels than multiple puffs for Cmax and Cav, and increased systemic β_2 responses on tremor, heart rate, and potassium levels. Single puffs with delayed inhalation produced significant decreases in plasma salbutamol levels and in systemic effects on tremor and heart rate but not potassium levels. The ratio between single puffs and single puffs with delayed inhalation for Cmax was 1.80-fold (95% CI 1.59 to 2.00).

Single puffs from the standard spacer produced a significant increase in Cmax compared with the antistatic treated spacer (both prewashed) with a ratio of 1.23 (95% CI 1.04 to 1.41), although no other differences were seen in average plasma salbutamol levels or systemic β_2 responses.

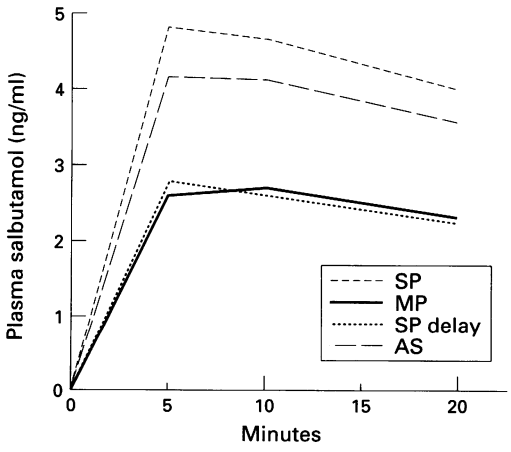

Figure 2 Mean plasma salbutamol concentration at five, 10, and 20 minutes after inhalation of 1200 µg salbutamol given as single puffs with spacer (SP), multiple puffs with spacer (MP), single puffs with a 20 second delay before inhalation from spacer (SP delay), and single puffs with an antistatic treated spacer (AS).

Discussion

Our results show that the use of multiple actuations and delayed inhalation from a Volumatic spacer both significantly reduce the lung bioavailability of salbutamol. This confirms previous in vitro work by Barry and O'Callaghan with salbutamol, sodium cromoglycate, beclomethasone dipropionate, and budesonide.[5-7 9] If these in vitro data with inhaled corticosteroids are reproduced in vivo it could be of considerable importance in the control of asthma. This may assume greatest relevance at doses of inhaled corticosteroid up

to 1000 μg/day since patients will in general be on the steep part of the dose–response curve for antiasthmatic efficacy.[12] A 20% difference in dose received could therefore have considerable impact on their disease control. It is also conceivable that patients could end up taking a greater number of puffs to achieve the same delivered dose, which will have significant long term cost and perhaps compliance implications.

Another important issue is drug delivery during an acute asthma attack. Due to reduced airway calibre and reduced lung deposition during an asthma attack, patients are likely to be at the steep part of the dose–response curve for bronchodilator efficacy of salbutamol. Indeed, this is the rationale for using high nebulised doses of β_2 agonist in this situation. As the use of multiple actuations in a spacer results in an approximate twofold reduction in the lung bioavailability of salbutamol, this should be taken into account in calculating the number of puffs required for acute bronchodilator relief.

We found that washing a Volumatic spacer is as effective as antistatic lining in reducing the effects of static charge on delivery of salbutamol in vivo. However, in vitro work with budesonide[7] or sodium cromoglycate[5] using the impinger method revealed that delivery of drug was more than doubled using a low static spacer compared with an unwashed new spacer. This highlights the importance of studying individual drugs and their various delivery devices, as it is not possible to extrapolate results from different studies.

The preparation and use of the Volumatic spacers during the study was intended to simulate what could be expected in normal clinical practice, since brand new spacers are not used each time a patient inhales their medication. Initially all the spacers were washed to try to reduce the effect of the high static charge which new spacers have been noted to carry,[13] as this may have reduced the amount of salbutamol recovered. Thus, for practical purposes a general practitioner who has a Volumatic spacer device for delivery of emergency high dose β_2 agonist therapy should prewash the spacer before its first use to reduce its high initial static charge.

In conclusion, we found that variations in technique of inhaling salbutamol via a Volumatic spacer have a substantial impact on its lung bioavailability with regard to delay in inhalation and multiple actuations, whereas an antistatic coating had no additional effect compared with washing the spacer.

We thank Static Safe Environments Ltd and TBA Industrial Products Ltd for their help in preparation of the antistatic treated spacers and Mrs J Orr for her assistance in preparation of the manuscript.

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