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Metal versus plastic spacers: an in vitro and in vivo comparison

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Abstract

This study compared the metal Nebuchamber® with the polycarbonate Volumatic® spacer in vivo as well as in vitro. Seventeen asthmatic patients were evaluated in a crossover placebo-controlled double-blind study. Bronchodilation, heart rate and serum potassium levels were measured at baseline and 15 min after administration of salbutamol. Cumulative dose-response curves (200, 400, 800 and 1600 μg) were constructed. The Andersen Cascade Impactor was used to compare the aerodynamic particle size distribution. The FEV_1 measurements showed highly significant differences between placebo and the two active preparations ($P < 0.001$), but not between the two active preparations ($P = 0.433$). The serum potassium levels also showed highly significant differences between placebo and the two active preparations ($P = 0.009$), but not between the two active preparations ($P = 0.532$). Only 1600 μg salbutamol dose raised the heart rate significantly, but the difference between the two active preparations was not significant. The in vitro deposition study revealed no significant differences in the delivered dose or in the fine particle dose ($P > 0.05$). In conclusion, there are no significant differences between the Volumatic® and Nebuchamber® either in vivo or in vitro.

Keywords: Volumatic®; Nebuchamber®; Salbutamol; In vitro; Bronchodilation

1. Introduction

Spacers were introduced to overcome the co-ordination problems people experience when using pressurised metered dose inhalers (pMDIs) (Kim et al., 1987; Koning, 1985; Levison et al., 1985). The majority of spacers are made from plastic materials (e.g. polycarbonate). Electrostatic charges at the surface of plastic spacers result in a decreased drug delivery to the lungs (Wildhaber et al., 1996a,b; Pierart et al., 1999). Several priming procedures have been shown to reduce that electrostatic charge. Coating the inner surface with surfactant after firing a placebo aerosol results in an increased lung deposition (Kenyon et al., 1998). Coating with household or ionic detergents has the same effect (Wildhaber et al., 1996a,b; Pierart et al., 1999). Despite these attempts to reduce the electrostatic charge of plastic spacers a non-electrostatic metal spacer was introduced (Bisgaard, 1995). The use of a metal spacer resulted in an improved drug delivery in vitro (Berg et al., 1998), and a better lung

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deposition in vivo compared to non-treated plastic spacers (Kenyon et al., 1998).

Up to now, no in vivo experiment is available which demonstrates the clinical superiority of the metal spacer over the conventional and less expensive, non-electrostatically charged plastic spacer. We therefore compared the bronchodilator effects and the systemic β_2-responses of salbutamol administered with a washed, and placebo primed polycarbonate spacer, versus a metal spacer. Also the in vitro characteristics of these combinations were measured.

2. Materials and methods

2.1. Study subjects

Seventeen asthmatic patients participated in the trial (11 women and six men). The average age (S.D.) was 36 (14) years, the mean forced expiratory volume in 1 s (FEV_1) (S.D.) was 87 (19)% of predicted. In all patients a bronchodilator response of $>9\%$ of predicted after inhalation of 400 μg salbutamol had been measured just before the trial. All but one used corticosteroids by inhalation. None of the patients were smokers. Except for the corticosteroids by inhalation, all regular medication was discontinued. Long acting β_2-mimetics were stopped 15 h, short acting β_2-mimetics 8 h and oral anti-asthma medication 24 h prior to the start of the study. All patients gave their written consent before the entry of the trial, which was approved by the hospital ethics committee.

2.2. Spacers

Two spacer devices were tested: a polycarbonate Volumatic® (750 ml; Glaxo Wellcome, UK) and a metal Nebuchamber® (250 ml; Astra Zeneca, Sweden). One day before the experiments, the polycarbonate spacers were washed thoroughly with household detergent, rinsed with warm water and air-dried. The spacers were also primed with 20 placebo puffs 0.5 h before administration of the first dose. Salbutamol 200 μg pMDIs (Ventolin®; Glaxo Wellcome, UK) were used as medication. The first ten actuations from each pMDI were fired to waste (primed). The pMDIs were pressed firmly into the spacer devices in order to avoid leakage at the connection site.

2.3. Study design

Seventeen asthmatic patients were evaluated in a crossover placebo-controlled double-blind study. Bronchodilation, heart rate and serum potassium levels were measured. In addition, the Andersen Cascade Impactor was used to compare the aerodynamic particle size distribution in vitro.

2.4. In vivo measurements

An in vitro study showed that multiple actuations of salbutamol into a Volumatic® spacer reduce the delivered dose and the fine particle dose (Barry and O'Callaghan, 1994). Therefore, cumulative single actuations were used in the present study to avoid possible negative effects.

Each patient visited the lung function laboratory three times with intervals of one week. The baseline FEV_1 was not allowed to vary more than 10% between the sessions. Each session consisted of measurements of all parameters at baseline and 15 min after each dose of salbutamol. Cumulative doses of 200, 400, 800 and 1600 μg were administered. The inhalation manoeuvre consisted of a slow breath with a flow of 40–60 l min^{-1} from residual volume (RV) to total lung capacity (TLC), followed by a breath-holding period of 10 s. The pMDI was shaken 10 s between each inhalation. A double-dummy technique was used to avoid bias due to differences in the spacers.

The FEV_1 was measured by means a pneumotach (SensorLoop; SensorMedics, the Netherlands). Per determination three readings were taken, and the best of three selected. The systemic β_2-responses were measured as change in heart rate, and decrease in serum potassium level. The heart rate was determined by manual counting over a period of 60 s. Serum potassium levels were measured by taking blood samples from a cannula in an antecubital fossa vein, and subsequent analysis by means of flame photometry.

2.5. In vitro measurements

The aerodynamic particle size distribution of salbutamol 200 μg pMDIs through the spacers was measured with an Andersen Cascade Impactor (Andersen 1 ACFM Non-Viable Ambient Sampler, Copley, UK) using the USP throat as entry port. The cut-off diameters were 9.0, 5.8, 4.7, 3.3, 2.1, 1.1, 0.7, and 0.4 μm for stage 0 up to 7, respectively. The impactor plates were coated with 2% viscous silicon oil in hexane in order to prevent bouncing of dried particles. A flow rate of 28 l min^{-1} was applied during 5 s per actuation. The spacers were prepared similar to the in vivo protocol. Four actuations were separately introduced into the spacer, which was attached to the impactor. The pMDI was shaken for 10 s between actuations. The aerodynamic particle size distribution was performed in quadruplicate.

The mouthpiece of the actuator, the spacer, mouthpiece adaptor, throat, stage 0 up to 7 and the filter were rinsed with methanol:water (15:85 v/v) containing 0.001% w/v fenoterol hydrobromide as an internal standard. The amount of salbutamol was determined by HPLC using an 125 × 4 mm Hypersil BDS 5 μm C18 column with guard column (Hewlett Packard), and a detection wavelength of 278 nm. Each sample was analysed in triplicate.

2.6. Statistical analysis

The lung function was expressed as a percentage of the predicted value. Three dose-response curves were generated in the in vivo study: two for the pMDI with spacer sessions and one for the placebo session. These dose-response curves were analysed for effects related to the type of spacer (spacer-effect), effects of increasing dosages (dose-effect), and interaction between spacer and dosage using repeated measurements analysis of variance.

The in vitro experiments were performed in quadruplicate. The fine particle dose was calculated as cumulative amounts deposited on stages 3 up to 7 and the filter (particles ≤ 4.7 μm). The delivered dose was determined by addition of the fine particle dose, and the amounts deposited in the mouthpiece adaptor, throat, stage 0, stage 1, and stage 2. The metered dose was calculated by addition of the delivered dose and the amounts deposited in the mouthpiece of the actuator and the spacer device. Statistical significant differences in deposition profiles were analysed by using a Student's t-test. In all calculations an α-value of < 0.05 was considered as being significant.

3. Results

3.1. In vivo results

All patients completed the three sessions. The interaction between dose and preparation was highly significant ($P < 0.001$) for all parameters, indicating that the dose-response curves for the placebo and active preparations did not run parallel.

The evaluation of the spacers with respect to FEV_1 measurements showed highly significant differences between placebo and the two active preparations ($P < 0.001$), but not between the two active preparations (Fig. 1, $P = 0.433$). The actual FEV_1 difference between the two active preparations was only 0.562% of the predicted value (95% CI −0.920–2.045%). The dose-effect evaluation

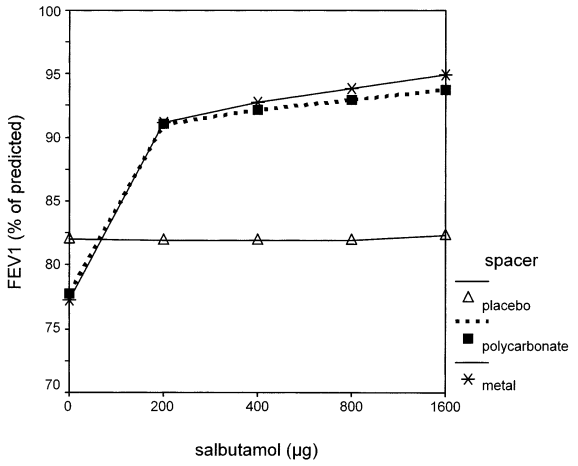

Fig. 1. Relationship between cumulative doses of salbutamol and forced expiratory volume in one second (FEV_1; in % of predicted) in asthmatic patients. The FEV_1 was measured at baseline (0 μg), and 15 min after each dose (200, 200, 400 and 800 μg) of salbutamol.

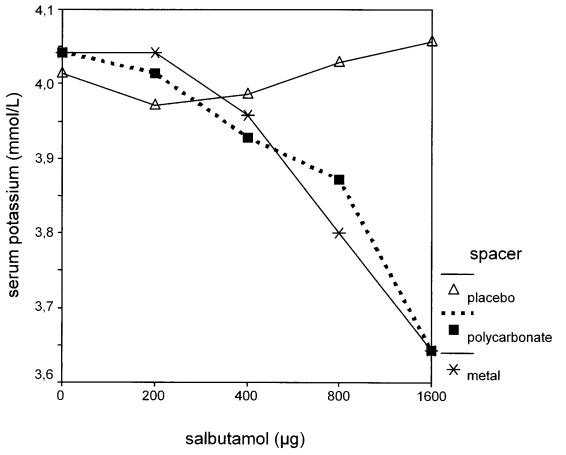

Fig. 2. Relationship between cumulative doses of salbutamol and serum potassium levels (in mmol l^{-1}) in asthmatic patients. The serum potassium level was measured at baseline (0 µg), and 15 min after each dose (200, 200, 400 and 800 µg) of salbutamol.

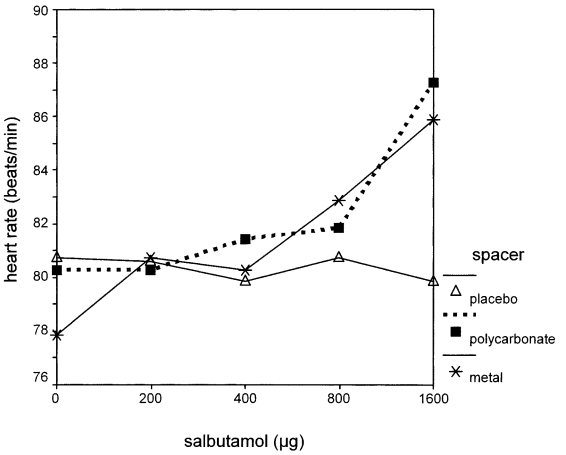

Fig. 3. Relationship between cumulative doses of salbutamol and heart rate (in beats min^{-1}) in asthmatic patients. The heart rate was measured at baseline (0 µg), and 15 min after each dose (200, 200, 400 and 800 µg) of salbutamol.

showed that each subsequent dose elicited a stronger bronchodilation than the previous dose (P-values for all next dose steps < 0.001).

The evaluation of the spacer-effect in case of the serum potassium showed similar outcomes as for the FEV_1 (Fig. 2). The difference between the two active preparations was -0.036 mmol l^{-1} (95% CI -0.158–0.085 mmol l^{-1}). The dose-effect evaluation showed that the serum potassium decrease from baseline was significant starting from the 800 µg dose ($P = 0.009$; P-value for 800 vs. 1600 µg dose < 0.001).

The heart rate after placebo showed a small, but significant linear decrease of 4 beats min^{-1} (Fig. 3, $P = 0.008$). After inhalation of the active preparations a significant increase in heart rate was noted due to the increasing dosages, but only the 1600 µg dose raised the heart rate significantly ($P = 0.003$) with 6 beats min^{-1} (95% CI 2.5–9.6 beats min^{-1}). The difference of 1 beat min^{-1} between the active preparations was not significant ($P = 0.469$, 95% CI -2–4 beats min^{-1}).

3.2. In vitro results

The combination of the salbutamol pMDI and the metal Nebuchamber® showed no significant difference in deposition in the spacer plus the mouthpiece of the actuator compared to the polycarbonate Volumatic®: 127.1 ± 12.5 µg resp 138.3 ± 16.7 µg (Fig. 4, Table 1, $P = 0.324$). For the Volumatic® most drug (104.4 ± 14.6 µg) was recovered from the spacer itself, while for the Nebuchamber® more drug was found on the

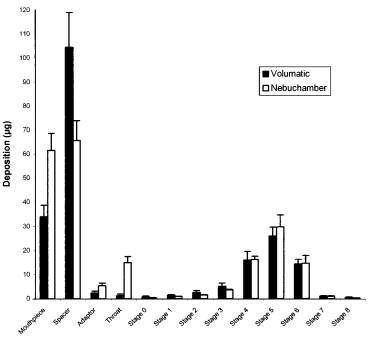

Fig. 4. The aerodynamic particle size distribution of salbutamol 200 µg pMDIs through the Volumatic® (■) and Nebuchamber® (□) measured with an Andersen Cascade Impactor. The cut-off diameters were 9.0, 5.8, 4.7, 3.3, 2.1, 1.1, 0.7, and 0.4 µm for stage 0 up to 7 respectively. No significant differences were observed in the fine particle dose (≤ 4.7 µm) from the Nebuchamber® and Volumatic® ($P = 0.717$). The amount of salbutamol on stage 3 to stage 8 also did not differ significantly (all P-values > 0.06), in contrast to the deposition on stage 0, stage 1, stage 2 as well as on the mouthpiece adaptor and the throat of the impactor (all P-values > 0.05).

Table 1
Salbutamol drug deposition comparison experiments of the Volumatic® and the Nebuchamber® from an Andersen Cascade Impactor

	Volumatic®	Nebuchamber®
Metered dose	209.2 μg±16.4 μg	215.6 μg±12.8 μg
Mouthpiece/actuator	33.9 μg±4.7 μg	61.5 μg±7.1 μg
Spacer (without mouthpiece)	104.4 μg±14.6 μg	65.6 μg±8.3 μg
Total spacer deposition	138.3 μg±16.7 μg	127.1 μg±12.5 μg
Delivered dose	70.9 μg±13.2 μg	88.5 μg±11.5 μg
Fine particle dose ($\leq$4.7 μm)	62.8 μg±5.6 μg	65.5 μg±6.0 μg

mouthpiece of the actuator (61.5±7.1 μg). The dose delivered to the impactor was 88.5±11.5 μg for the Nebuchamber® and 70.9±13.2 μg for the Volumatic® (Table 1, $P = 0.09$). No significant differences were observed in the fine particle dose ($\leq$4.7 μm) from the Nebuchamber® and Volumatic®: 65.5±6.0 versus 62.8±5.6 μg (Table 1, $P = 0.717$). The amount of salbutamol deposited on stage 3 to stage 8 also did not differ significantly (all P-values > 0.06), in contrast to the deposition on stage 0, stage 1, stage 2 as well as on the mouthpiece adaptor and the throat of the impactor (all P-values > 0.05).

4. Discussion

We compared the clinical response in asthmatic adults to salbutamol from a washed and primed polycarbonate Volumatic® spacer and a metal Nebuchamber®. In addition, a cascade impactor was used to compare the in vitro aerodynamic particle size distribution. The in vivo study did not show significant differences in bronchodilation or systemic β_2-responses. The in vitro study revealed no significant differences in delivered and fine particle dose.

Previously, a stronger bronchodilation was shown with the polycarbonate Volumatic® after reducing charge with a detergent, while priming with a placebo increased the lung deposition (Wildhaber et al., 2000; Kenyon et al., 1998). Measuring residual charge is difficult and to ascertain that no charge was left, the Volumatic® was washed and primed. In daily life patients, who wash and use their spacer frequently, also 'wash and prime' and reduce charge effectively.

Failure to find a significant in vivo difference between the two combinations cannot be attributed to a lack of discriminatory power of this study. Highly reversible asthmatics were selected and each next dose resulted in a small but detectable increase in lung function. This, combined with a sufficient large sample size, resulted in a high statistical power of the study.

The small in vivo and in vitro differences found, indicate that modification by these two spacers of the cloud emitted by the pMDI, is comparable. An earlier lung deposition study of a budesonide (Pulmicort®) pMDI, used either with a Volumatic® or Nebuchamber® spacer, resulted in the same deposition pattern as in our study: similar fine particles fractions, a lower actuator and higher spacer deposition for the Volumatic® (Kenyon et al., 1998). The higher deposition in the Volumatic® compared to the Nebuchamber®, and the fact that the fine particle fraction is identical, indicates that the large particle emission is lower with the Volumatic®. The large particles emitted by the Nebuchamber® deposit in the oropharynx. This pattern was also found in our in vitro data: the throat deposition in the impactor was higher with the Nebuchamber®. Since two different pMDIs (Pulmicort® and Ventolin®) show the same deposition patterns, it is unlikely that the pMDI or the way it is connected to the spacer is the source of these patterns. During the in vivo as well as the in vitro experiments the pMDIs were pressed firmly into the spacer devices in order to avoid leakage. It is unlikely that the difference in mouthpiece deposition is caused by inappropriate attachment of Ventolin® to the Nebuchamber®.

In the past much attention focussed on the volume and shape of spacers and most reports indicate that a small volume spacer delivers less drug to the lungs. The Volumatic® is three times larger than the Nebuchamber®, and the valve design is different. The fact that the smaller Nebuchamber® delivers the same amount of drug to the airways as the larger Volumatic®, illustrates that volume is not the sole factor influencing drug delivery: valve deposition might

be an additional factor. The high velocity of the cloud will favour impaction of the largest particles and after that the cloud will impact on the valve during inhalation. These two portions are generally reported as the spacer deposition, but the individual contribution of each remains unknown. It is now conceivable that spacer volume will influence the magnitude of the first portion, but not of the second. A small spacer with adequate valves would be have similar to a large spacer with a less well designed valve. The volume-effect is determined by the velocity of the aerosol cloud: Barry showed that a slower moving aerosol cloud deposits less (Barry and O'Callaghan 1994). This effect is less important after removing electrostatic charge (Barry and O'Callaghan, 1997).

We found a slightly higher delivered dose for the Nebuchamber® in vitro, which is clinically less relevant because that part of the dose consists of inefficacious non-respirable particles. The fine particle fraction is the same so the differences must consist of larger particles. Studies measuring the delivered dose by imposing a filter between the patient and the spacer device and measuring the mass on the filter do not take this into account (Janssens et al., 1999). Obviously, such data cannot be used well to predict the clinical effect. The amount of drug in the lungs seems to be a good parameter, and differences between masses deposited indicate differences in bronchodilation. Newman, however, found that it takes large differences in drug delivery to demonstrate a clinically relevant difference in bronchodilation (Newman et al., 1991).

Our study revealed that the dose-response curve of salbutamol administered with a pMDI in combination with a spacer climaxes at a 200 μg dose. Both pMDI combinations with Volumatic® and the Nebuchamber® have negligible systemic side effects at this dose. Subsequent administrations showed only a marginal difference in the bronchodilator effect, unlike the increased systemic β_2-responses.

To summarize, we conclude that a washed and placebo primed large volume polycarbonate Volumatic® spacer is interchangeable with a small volume metal Nebuchamber® in vivo as well as in vitro.

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