

A non-electrostatic spacer for aerosol delivery

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Abstract

A pear shaped non-electrostatic spacer, composed of steel with a volume of 250 ml and equipped with a facemask containing integrated inlet and outlet valves for inspiration and expiration, was compared with three plastic spacers. The plastic spacers were primed with repeated puffs from a budesonide pressurised metered dose inhaler (p-MDI) to minimise the electrostatic charge on the plastic. The procedure prolonged the half life ($t_{1/2}$) of the aerosol in the Nebuhaler from nine to 32 seconds. A normal cleaning procedure reduced the aerosol $t_{1/2}$ back to baseline. The $t_{1/2}$ of the aerosol in the metal spacer was 27 seconds and independent of the use of p-MDI. In vitro the maximum dose of budesonide from a p-MDI, expressed as a percentage of the nominal dose, was 56% from the non-electrostatic spacer, 61% from the Nebuhaler, 45% from the Babyhaler, and 30% from the Aero-Chamber. In 124 children, age 6 months to 6 years, suspected to have asthma the non-electrostatic spacer delivered a mean total dose of budesonide aerosol of 39% of the nominal dose, which was significantly higher than the Babyhaler (28%), the Nebuhaler (21%), and the AeroChamber (19%). These differences were most pronounced in children younger than 4 years. The improved dose delivery from the small volume non-electrostatic spacer is probably related to the non-electrostatic spacer material and the valves which assured unidirectional airflow from the spacer without adding any dead space in the inspiratory channel. The non-electrostatic spacer should improve the cost effectiveness of aerosol treatment and, as the counteracting effects of priming and recharging of the plastic from cleaning are avoided, should deliver a more reliable dose.

(*Arch Dis Child* 1995; 73: 226-230)

Keywords: spacer, aerosol, pressurised metered dose inhalers.

Pressurised metered dose inhalers (p-MDI) coupled to a spacer system with a facemask provide convenient aerosol delivery to young children and offer obvious advantages over jet nebulisers.¹⁻³ In recent clinical trials such devices have proved their efficacy in treatments with inhaled β_2 agonists⁴⁻⁶ and inhaled steroids.⁷⁻⁹ However, when these devices are used, due regard should be given to the low tidal volume and tidal flow of young children. In previous communications we have suggested

a spacer of small volume, manufactured in steel, with separate inspiratory and expiratory valves and a minimised dead space in the inspiratory channel. This prototype was found to provide an efficient dose delivery of approximately 38% of the nominal dose independent of age in young children aged between 6 months and 6 years.^{2,3} The steel provides non-electrostatic surfaces and assures, together with the small volume, a highly concentrated aerosol with a slow passive disappearance within the spacer independent of the counteracting effects of priming from repeated use of p-MDI or washing procedures. The two one way valves assure unidirectional breathing, with inspiration from the spacer and expiration to the outside. The minimised dead space of the valve system reduces the loss of aerosol during expiration. A spacer based on these principles is now becoming commercially available. We set out, therefore, to compare this steel non-electrostatic spacer with other feasible alternatives with respect to aerosol delivery in young children. The AeroChamber has gained widespread use for the treatment of young children,⁵ and the Babyhaler was introduced recently for a similar purpose.⁶ The Nebuhaler, with inactivated valve, has been recommended as a more simple device for babies.¹⁰ In the present study we compared these devices with respect to the delivery of budesonide p-MDI in vitro and in vivo. The quality of the aerosol was compared in vitro in terms of the particle size distribution and the half life ($t_{1/2}$) of the airborne aerosol. The quantity of the aerosol delivery was compared in vivo in terms of the total dose delivered in a group of 124 young children with suspected asthma, aged between 6 months and 6 years.

Methods

Budesonide p-MDI (Astra AB) at 200 μ g/dose was used as the tracer in the study of four different spacer models:

(A) A new prototype was made of steel, has a volume of 250 ml, and is pear shaped (fig 1). The valve system consists of two unidirectional valves which are orientated in opposite directions. The inspiratory valve is a flapvalve which opens from the centre. This valve system adds no dead space to the facemask because the inspiratory valve opens into the facemask, the expiratory valve opens from the facemask to the exterior, and both are integrated into the mask. The pressure drop required to open the valve is 100-125 Pa at a flow rate of 15 l/min (data on file). The spacer was equipped with a silicone Laerdal (Norway) facemask. The prototype spacer was produced by Astra AB, Sweden.

(B) An AeroChamber produced by Trudell Medical (Canada) in which the spacer material

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Accepted 15 May 1995

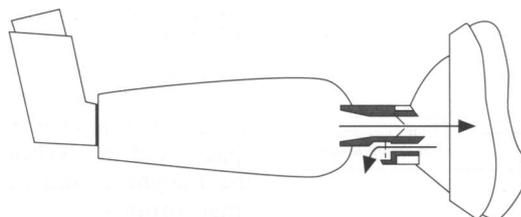


Figure 1 The non-electrostatic spacer. A 250 ml spacer manufactured in steel and equipped with a facemask. Inlet and outlet valves are integrated into the facemask. This arrangement of the valves adds no extra dead space to the inspiratory channel. A filter holder containing a filter was interposed between the facemask and the inspiratory valve during the trial.

is plastic and has a volume of 145 ml. A single one way valve and open holes in the facemask (which are intended for expiration) constitute the valve system. This adds no dead space to the facemask. The pressure drop required to open the inspiratory valve is 25–30 Pa at a flow rate of 15 l/min (data on file). The spacer was used with its original cone shaped silicone facemask.

(C) A Babyhaler produced by Glaxo UK along the principles suggested by Kraemer *et al.*⁶ The spacer is made of polycarbonate, has a volume of 350 ml, and is equipped with inlet and outlet valves. The dead space between the inspiratory and the expiratory valve is 40 ml. The pressure drop required to open the inspiratory valve is 10 Pa at a flow rate of 15 l/min (data on file). The expiratory valve opens to the exterior and closes spontaneously at zero flow. The spacer was equipped with a silicone Laerdal facemask.

(D) A Nebuhaler (Astra AB, Sweden) used for babies along the principles suggested by O'Callaghan *et al.*¹⁰ The spacer is composed of polycarbonate and has a volume of 750 ml. The valve system is inactivated by gravity because the spacer is held at a 45° angle to the horizontal, which causes the spacer volume to function as a rebreathing bag. The spacer was equipped with a simple cone shaped facemask of thermoplastic elastomer, comparable in design with that of the AeroChamber.

IN VITRO STUDIES

The maximal dose obtainable from the spacers was regarded as the mean dose collected on filters (Vital Signs), which were placed between the inspiratory valve and the evacuation pump. The budesonide aerosol was evacuated from the spacer through the filter by a flow of 30 l/min for 10 seconds, starting two seconds after actuation of the p-MDI. Measurements were repeated on three specimens of each spacer, with five doses in each. The amount of aerosol ejected by the jet through the valve systems upon actuation of the p-MDI was estimated by collecting the filters after actuation of the spray but without evacuation of the spacers (n=12). An average of less than 3 µg out of 200 µg of aerosol was thus lost from each spacer system. This fraction was not considered any further in this method. The filter retained more than 99% of the aerosol, as less than 0.1% of the initial dose of budesonide could be found on a second

filter added in series in a pilot study. The pressure drop over the filter is 230 Pa at 60 l/min. The dead space of the filter holder is 20 ml. The filter and filter holder were washed with ethanol, and analysed for budesonide content with a reverse phase liquid chromatographic system (C18 column with ethanol/water as the mobile phase). The dose delivery from the non-electrostatic spacer was studied by repeating 100 dose deliveries through the non-electrostatic spacer from a single canister containing 100 doses.

The mass median aerodynamic diameter (MMAD), and the kinetics of the budesonide aerosol within the spacers, were analysed using an Anderson sampler with a throat (US pharmacopoeia), without a preseparator, at a flow of 28 l/min. The fractionated aerosol was eluted and quantified by reverse phase liquid chromatography. Droplets smaller than 4.7 µm were termed small droplets. The aerosol was evacuated from the spacer at 2, 5, 10, 30, and 60 seconds after actuation of the spray. The aerosol remained passively in the spacer between actuation and the time of evacuation. The $t_{1/2}$ of the aerosol airborne in the spacer was estimated from a semilogarithmic relation of the total dose as well as the small particle dose versus time.

The effect of priming the non-electrostatic spacer and the Nebuhaler was studied by determining the $t_{1/2}$ in the unused non-electrostatic spacer and Nebuhaler and comparing with the $t_{1/2}$ after the spacers had been primed with 15 puffs of budesonide at 200 µg/dose the previous day. The effect of the recommended washing procedure in mild detergent was examined by estimating $t_{1/2}$ after washing a primed spacer. These measurements were repeated in three specimens of each spacer, with five doses in each.

IN VIVO STUDIES

Young children between 6 months and 7 years old who were suspected of having asthma were eligible for the study. Asthma was suspected from recurrent wheezing and coughing which could be stopped with an inhaled β_2 agonist. The children were recruited from those who had previously used a spacer with a facemask. The children were excluded if they presented with respiratory symptoms on the study day.

The study was designed as a controlled, randomised, single centre, crossover study. The children respired twice from each device in a randomised order. After the spacer had been used by three children it was replaced with another primed spacer. All spacers had been primed by actuating 15 puffs of budesonide over five minutes into the spacer the previous day. The budesonide p-MDI to be inserted into the spacer was shaken immediately before use. The spacer was held in place before actuation of the p-MDI and care was taken to guarantee a close fit of the facemask. The child respired through the spacer for 60 seconds. Passive cooperation was sought during the procedure by allowing the child to sit with a parent and watch video films. The

Table 1 *In vitro* results

	$t_{1/2}$ of aerosol in the primed spacers (sec)		Dose of aerosol from the primed spacers (% of nominal dose)		Fraction of small particles from the primed spacers, after 2 seconds (% of total dose of budesonide aerosol)
	Total dose	Small particles	Mean	CV	
Non-electrostatic spacer	27	33	56	13	68
Babyhaler	21	23	45	18	79
Nebuhaler	32	39	61	7	69
AeroChamber	17	19	30	18	80

compliance of the child was noted in each case. The dose of budesonide aerosol delivered from the spacer to the child was measured by interposing a filter (Vital Signs) between the face-mask and the valve system of the spacers.

The study was open to the patient and to the investigator with regard to the devices and filters, but blind to the analysing laboratory. The randomisation code was not broken until all data had been analysed and a clean file had been declared by the study monitor, who also verified source data and drug accountability. The study was performed in accordance with the Declaration of Helsinki and was accepted by the local ethics committee (KA93120). All parents gave their informed consent.

STATISTICAL METHODS

Central tendency was represented by the mean value and the scatter by the SD. The precision is estimated as the coefficient of variation (CV) which was calculated as the SD as a percentage of the mean. Each observation is the average of two observations for each subject on each device. Children were classified in age groups of 0–2 years, 2–4 years, and 4–6 years. The comparison of dose delivery was performed using within-patient comparisons in a general linear model for each of the three age groups. A multiple comparison procedure was applied to maintain the overall significance level. Age dependency was evaluated by the distribution free Jonckheere-Terpstra test. All statistical tests were performed using $\alpha=0.05$.

Results

Dose delivery of the spacers *in vitro* is given in table 1 together with the $t_{1/2}$ of the aerosol and the fraction of small particles.

The MMAD of the aerosol from the

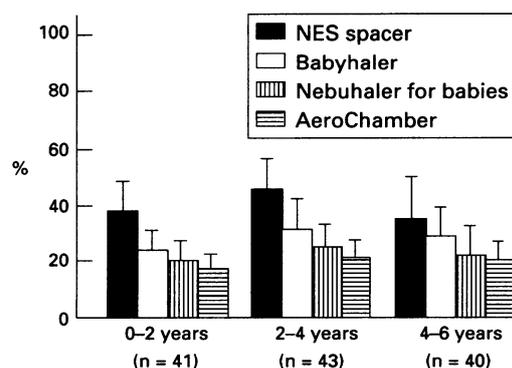


Figure 2 Dose delivery from the non-electrostatic (NES) spacer, Babyhaler, Nebuhaler for babies, and AeroChamber.

non-electrostatic spacer, the Nebuhaler, the Babyhaler, and the AeroChamber was between 3.4 μm and 3.9 μm two seconds after actuation of the sprays. At this time, 68–69% of the budesonide aerosol from the non-electrostatic spacer and the Nebuhaler, and 79–80% from the Babyhaler and the AeroChamber, was in small droplets of less than 4.7 μm diameter. These percentages increased in parallel over time for all the spacers.

The CV% in the non-electrostatic spacer was unchanged (14%) when 100 doses were repeated from a single canister.

The $t_{1/2}$ of the total dose of budesonide aerosol was nine seconds in an unused Nebuhaler, which increased to 32 seconds if the spacer was primed with 15 puffs and left overnight. After washing the spacer, the $t_{1/2}$ of the budesonide aerosol assumed the characteristics of an unused spacer ($t_{1/2}=14$ seconds). Despite priming, the Babyhaler and the AeroChamber provided a $t_{1/2}$ of only 21 and 17 seconds respectively. The $t_{1/2}$ in the non-electrostatic spacer was 27 seconds and was unaffected by priming or washing procedures; $t_{1/2}$ of the small particle dose in primed spacers showed similar differences (table 1).

The study was completed by 124 children: 20 aged 6–11 months, 21 aged 12–23 months, 23 aged 24–35 months, 20 aged 36–47 months, 19 aged 48–51 months, and 21 aged 52–83 months. There were 48 girls and 76 boys.

No significant monotone age dependent dose delivery was found (fig 2). The children obtained a mean total dose of budesonide aerosol of 39%, 21%, and 28%, and 19% from the non-electrostatic spacer, the Nebuhaler, the Babyhaler, and the AeroChamber respectively (table 2). The dose delivery from the non-electrostatic spacer was significantly higher than that of the other spacers in the age groups of 0–2 years and 2–4 years, $p<0.0001$ in both groups. In the age group of 4–6 years the difference between the non-electrostatic spacer and the other spacers was only significant at a level of $\alpha=0.05$. The dose delivery from the Babyhaler was significantly higher than that from the AeroChamber in the age groups of 0–2 years and 2–4 years; $p<0.001$ in both groups.

The dose scatter *in vivo* was comparable in the four devices, with CV ranging from 31% in the AeroChamber to 40% in the Nebuhaler for babies (table 2). This scatter was not reduced significantly by withdrawing the children who opposed the procedure.

Discussion

The dose of aerosol available to inhalation from p-MDI via a spacer is influenced by the (1) passive disappearance of the aerosol, (2) initial dose available, and (3) valve control of the inspiration and expiration. The passive disappearance of the aerosol from the air in the chamber, as estimated by the $t_{1/2}$, will be affected by the material of the spacer wall and the priming effect of any previous use of spray or recharging of the plastic from cleaning

Table 2 *In vivo* results from primed spacers

	Dose of aerosol (% of nominal dose)	
	Mean	CV
Non-electrostatic spacer	39	36
Babyhaler	28	34
Nebuhaler	21	40
AeroChamber	19	31

procedures. In this study we found that the $t_{1/2}$ increased from nine seconds in an unused polycarbonate spacer (Nebuhaler) to 32 seconds after use of 15 puffs of budesonide. However, this priming effect was reduced and the $t_{1/2}$ fell towards baseline values after a normal cleaning procedure. The counteracting effects of repeated use of the spacer and intermittent cleaning procedures are, therefore, likely to affect the $t_{1/2}$ of the aerosol and thereby the dose delivery from the spacer unpredictably. Similar confounding effects may occur in other spacers made of plastic materials. The mechanism behind the reduced $t_{1/2}$ in plastic spacers is probably that of electrostatic attraction between the material and the charged aerosol. Accordingly, antistatic treatment of a plastic spacer increased the $t_{1/2}$ of an aerosol of cromoglycate generated from a p-MDI.¹¹ The $t_{1/2}$ in the steel non-electrostatic spacer was not affected by priming and the dose delivery was constant throughout the use of a canister of 100 doses. The time available for inhalation is longer and more predictable and, therefore, the dose delivery can be expected to be larger and more stable over time with an non-electrostatic spacer than with a plastic spacer.

The total dose available *in vitro* as a percentage of the nominal dose present immediately after actuation was related to spacer volume in the 750 ml Nebuhaler (61%), the 350 ml Babyhaler (45%), and the 145 ml AeroChamber (30%). However, the 250 ml non-electrostatic spacer provided 56% of the nominal dose. The choice of spacer size has to balance the need for a small volume (to match the tidal volume of the infant or young child), with the loss of aerosol through impaction, which will be greater in a small volume spacer. However, loss through adsorption to the walls of the spacer together with the shape of the spacer will also affect the initial dose available for inhalation. Accordingly, the non-electrostatic spacer provided a high dose relative to its small volume which is probably a result of the lack of electrostatic attraction between the aerosol and the spacer material.

In vivo, the children obtained a mean total dose of budesonide aerosol of 39%, 28%, 21%, and 19% from the non-electrostatic spacer, the Babyhaler, the Nebuhaler, and the AeroChamber respectively. The dose delivery from the non-electrostatic spacer was significantly higher than that of the other spacers, and was most pronounced in children less than 4 years old (fig 2). The Babyhaler provided a significantly higher dose than the AeroChamber in children less than 4 years old. The dose delivery of 39% of the nominal dose from the non-electrostatic spacer corresponds

remarkably well with our previous findings where the early prototype, based on similar principles, delivered 38% of the nominal dose to 164 children of a comparable age distribution.^{2,3}

It appears that the delivered dose *in vivo* is approximately two thirds of that found *in vitro* with the exception of Nebuhaler where the *in vivo/in vitro* relation was one third only. This difference is probably related to the lack of valve control in this application of the Nebuhaler for babies,¹⁰ which causes the children to exhale through the spacer, thus expelling part of the aerosol. In a previous report we documented a pronounced age related dose delivery from the Nebuhaler in young children aged 6 months–6 years.^{2,3} However, in that situation the spacer was held in a horizontal position which allowed the valve to function for older children and delivered approximately 44% of the nominal dose to this group. Younger children were unable, apparently, to activate the valve reliably and therefore received just 19% of the nominal dose. In the present application the spacer was held at a 45° upward angle which also inactivated the valve so an age independent, but very low, dose of 21% was obtained.

The large dead space of 40 ml of the Babyhaler valve system is a likely cause of the reduced mean dose delivery from this device, as the last 40 ml of each inhalation is trapped between the inspiration and exhalation valve and is subsequently exhaled.

The filter holder interposed between the facemask and the valve adds 20 ml of dead space between the valve and the filter, which will cause an underestimation of the aerosol delivery. This is because the last 20 ml of the inhalation does not reach the filter, but is exhaled during the next expiration. The dead space of the delivery system, including the filter holder, constitutes an increasing fraction of the tidal volume in lower age groups and would tend to cause an inverse relationship between age and the dose delivered. However, not even the Babyhaler with its large extra dead space of 40 ml between the valves, produced a significant age dependent dose delivery. This is probably a result of the fact that young children hyperventilate within a facemask, which is in agreement with our previous findings.^{2,3}

The dose collected on the filter interposed between the facemask and the spacers is not an accurate measure of the dose deposited in the lungs, but it reflects the dose of budesonide aerosol delivered at the child's mouth as the end point of the delivery system. If the method is extended with *in vitro* measurements it may give an indication of the actual dose available for inhalation into the lower airways. Two seconds after actuation, the dose of budesonide aerosol carried *in vitro* in droplets of less than 4.7 µm diameter was 68–69% in the non-electrostatic spacer and the Nebuhaler for babies, and 79–80% in the Babyhaler, and the AeroChamber. The fraction of small droplets increased in parallel during the subsequent minute in all four spacers. A conservative

estimate of the dose of small droplets available for inhalation may, accordingly, be approximated by multiplying the percentage of such droplets (as measured in vitro two seconds after actuation) with the total dose (as measured in vivo). The rank order of dose in small droplets as a percentage of the nominal dose is then: non-electrostatic spacer (27%), Babyhaler (22%), and Nebuhaler for babies and AeroChamber (both 15%). This approximation suggests that the dose delivered to the lower airways will be almost doubled by using the non-electrostatic spacer instead of a Nebuhaler for babies or an AeroChamber. This difference is probably of clinical relevance, at least with regard to the potency of the treatment with inhaled steroids.

The scatter of the dose delivery appeared to be similar between the devices in vivo, with CVs between 31% and 40%. It would be desirable to improve the scatter of the dose delivery in future improvements of devices for aerosol treatment of young children.

Budesonide was used as the tracer, but other steroids may behave differently in the various spacers, and different p-MDIs may also affect the performance of the aerosol delivery. The findings may not extrapolate to non-steroids.

In conclusion, the small volume, steel non-electrostatic spacer with separate inlet and outlet valves integrated into the facemask and no dead space provided a significantly higher dose than the plastic spacers. This was most pronounced in children younger than 4 years. The estimated dose delivery in small droplets from the non-electrostatic spacer was approximately double that of the delivery from the Nebuhaler for babies or the AeroChamber. The Babyhaler provided an intermediate dose. The improved dose delivery from the small volume non-electrostatic spacer is probably

related to the non-electrostatic spacer material and the valves assuring unidirectional airflow from the spacer without adding any dead space in the inspiratory channel.

This effect of device on the potency of the drug treatment is obviously important and such differences between devices may serve as an example of the need to specify the delivery device in the dose recommendations. All the spacers tested provided dose delivery which was not related to the age of the child. Each device is, in its own right, a useful delivery device for the treatment of young children, although the counteracting effects of priming and cleaning may be disadvantageous with the electrostatically active plastic spacers.

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