Effect of electrostatic charge, flow, delay and multiple actuations on the in vitro delivery of salbutamol from different small volume spacers for infants

Johannes H Wildhaber, Sunalene G Devadason, Ernst Eber, Mark J Hayden, Mark L Everard, Quentin A Summers, Peter N LeSouëf

Abstract

Background - A study was undertaken to determine the influences of electrostatic charge, flow, delay, and multiple actuations on the in vitro delivery of salbutamol generated by a pressurised metered dose inhaler (pMDI) from small volume spacers used in infants.

Methods - Ten actuations from a salbutamol pMDI were drawn at different flow rates after either single or multiple actuations, with or without delay, through either static or reduced static spacers. An ionic detergent was used to reduce the charge of plastic spacers (Babyhaler, Babyspacer, Aerochamber, Nebuhaler). Electrostatic charge was measured using an electrometer. A multistage liquid impinger was used to determine the particle size distribution of the output of the pMDI through the spacers.

Results - Electrostatic charge on the surface of plastic spacers had the greatest influence on delivery, causing a decrease in drug delivery. Reducing charge by coating the surface with ionic detergent resulted in an increase of 46.5%–71.1% (p<0.001) in small (<0.8 μm) particle delivery from small volume plastic spacers. Lower flow, delay, and multiple actuations resulted in decreased delivery from static spacers. Lower flow resulted in a decrease of 15% in small (<0.6 μm) particle delivery. Delay and multiple actuations resulted in a decrease of 40.7% and 76.0%, respectively, in small (<0.8 μm) particle delivery. The influences of lower flow, delay, and multiple actuations were greatly reduced or even eliminated by reducing charge. However, multiple actuations still resulted in a significant decreased delivery (p<0.05). The reduced static Nebuhaler had a higher delivery than all small volume spacers.

Conclusions - Electrostatic charge has a major influence on the delivery of salbutamol from small volume spacers. Using a metal spacer or ionic detergent coating of plastic spacers resulted in no or reduced charge and hence in improved delivery. Lower flow, delay, and multiple actuations played a major part only in static spacers.

Methods

Delivery of salbutamol generated by a pMDI (Ventolin, Allen and Hanburys, Australia) through three small volume plastic spacers (Babyhaler, Glaxo, Switzerland, 350 ml; Babyspacer, Astra, Denmark, 250 ml; Aerochamber, Trudell, Canada, 165 ml) and a small volume metal spacer (Nebuchamber, Astra, Sweden, 250 ml) was measured and compared with drug delivery through a large volume plastic spacer (Nebuhaler, Astra, Sweden, 750 ml).

To determine the effect of charge the plastic spacers were either rubbed with a piece of clear plastic to induce a high charge (static spacers) or immersed in diluted (1:250 with water) ionic detergent (Liquid Pyronet, Diversey, Australia) for one hour and subsequently dried for 24 hours to reduce charge by coating the inner surface with detergent (reduced static spacers). The electrostatic charge was measured using a slightly modified electrometer (Electronic Instruments Ltd, Model 37C; Jacoby Mitchell, Sydney, Australia). The 35 ml ionisation chamber was replaced by a metal
Reduced static

<table>
<thead>
<tr>
<th>Condition</th>
<th>Babyhaler</th>
<th>Babyspacer</th>
<th>Aerosol</th>
<th>Nebulizer</th>
<th>Nebuchamber</th>
</tr>
</thead>
<tbody>
<tr>
<td>Static</td>
<td>32.9 (1.45)%</td>
<td>30.3 (2.87)%</td>
<td>32.1 (2.06)%</td>
<td>31.0 (3.02)%</td>
<td>-</td>
</tr>
<tr>
<td>Reduced static</td>
<td>56.3 (2.05)%</td>
<td>44.4 (1.45)%</td>
<td>47.9 (2.03)%</td>
<td>63.7 (0.94)%</td>
<td>52.6 (4.69)%</td>
</tr>
</tbody>
</table>

The spacer was attached to a high performance multistage liquid impinger (MSLI, Copley, Nottingham, UK). Air was drawn through this system at a continuous flow rate of 60 l/min. The salbutamol pMDI was shaken for 30 seconds and two actuations were wasted prior to testing. Ten actuations were then introduced into the spacer with five second intervals between each actuation. The pMDI was shaken vigorously in the intervals between actuations.

In addition, the following procedures were performed for the Nebuchamber and the static and reduced static Babyhaler:

To determine the effect of flow, drug delivery was also measured at flow rates of 10 l/min and 30 l/min. The size distributions at a flow rate of 10 l/min were measured by mixing the flow from the spacer (10 l/min) with clean air at a flow rate of 20 l/min.

To assess the effect of delay on drug delivery, the continuous flow of 60 l/min was opened one, five, or 20 seconds after each actuation of the pMDI.

Drug delivery was measured after 10 single actuations at a continuous flow rate of 60 l/min, after five times two actuations, and after two times five actuations before opening the flow of 60 l/min immediately after the last actuation, respectively.

After actuating the pMDI the aerosol was drawn through the device with the entraining air flow. Droplets were deposited on the actuator, the throat, or one of the four stages. The total amount of the actuated drug was determined by the total recovery from the actuator, the spacer, the throat, and the four stages. The site of deposition in the MSLI was determined by the particle size of the droplets. The MSLI had been calibrated by the manufacturer (Astra Draco, Sweden) so that particles of >13 μm, 6.8–13 μm, 3.1–6.8 μm, and <3.1 μm for a flow rate of 60 l/min, and >18.4 μm, 9.6–18.4 μm, 4.4–9.6 μm, and <4.4 μm for flow rates of 30 l/min and 10 l/min were deposited on stages 1, 2, 3, and 4, respectively.

The actuator, spacer, throat, and each of the stages of the MSLI were separately washed with 40 ml of methanol. Five ml of 0.1 M NaOH was added to each wash and the volume was then made up to 50 ml with methanol. The absorbance (wavelength 246 nm) of each sample was measured in duplicate on a spectrophotometer (Hitachi U-2000, Japan). The concentration of salbutamol in each sample was obtained by using the absorbance of a standard solution containing a known concentration of salbutamol. The standard curve for salbutamol was linear (r² = 1.00) for concentrations between 0 and 21 μg/ml.

Each experiment was repeated four times and all measurements were undertaken under constant atmospheric conditions. The mean temperature was 22.6°C (range 21.8–24.7°C) and mean barometric pressure was 760 mmHg (range 750–768 mmHg).

Statistical analysis was carried out using analysis of variance (ANOVA) with a significance level of 95% (p<0.05).

Results
The electrostatic charge for static spacers was 3.3–6.7 μC/cm² and for reduced static spacers was 0–1.2 μC/cm².

The mean (range) of the total actuated dose was 1096 μg (1071–1111 μg) for the static

![Figure 1](http://example.com/figure1.png)

**Figure 1.** Mean (SD) delivery of particles of <6.8 μm as a percentage of the total actuated dose for the different spacers in static [■] and reduced static [□] conditions.

![Figure 2](http://example.com/figure2.png)

**Figure 2.** Mean (SD) delivery of particles of <9.6 μm as a percentage of the total actuated dose at flow rates of 30 l/min [■] and 10 l/min [□] for the static and reduced static Babyhaler and the Nebuchamber.
In vivo delivery of salbutamol to infants

Table 2  Mean (SD) and range of amount of particles of <9.6 μm diameter at flow rates of 10 l/min and 30 l/min and particles of <6.8 μm at a flow rate of 60 l/min delivered to stages 3 and 4 as a percentage of the total actuated dose for the static and reduced static Babyhaler and for the Nebuchamber

<table>
<thead>
<tr>
<th>Flow rate</th>
<th>Static Babyhaler</th>
<th>Reduced static Babyhaler</th>
<th>Nebuchamber</th>
</tr>
</thead>
<tbody>
<tr>
<td>Particles &lt;9.6 μm:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10 l/min</td>
<td>19.2 (2.92)%</td>
<td>62.4 (0.67)%</td>
<td>54.1 (1.52)%</td>
</tr>
<tr>
<td>(18.5-20.1)</td>
<td>(60.9-64.5)</td>
<td>(52.2-58.4)</td>
<td></td>
</tr>
<tr>
<td>30 l/min</td>
<td>22.6 (2.52)%</td>
<td>60.8 (0.55)%</td>
<td>54.1 (1.68)%</td>
</tr>
<tr>
<td>(21.9-23.2)</td>
<td>(59.7-63.4)</td>
<td>(51.9-57.7)</td>
<td></td>
</tr>
<tr>
<td>Particles &lt;6.8 μm:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>60 l/min</td>
<td>32.9 (1.45)%</td>
<td>56.3 (2.05)%</td>
<td>52.6 (4.69)%</td>
</tr>
<tr>
<td>(31.1-34.6)</td>
<td>(54.3-57.2)</td>
<td>(48.4-57.4)</td>
<td></td>
</tr>
<tr>
<td>Delay 1 second</td>
<td>19.5 (1.91)%</td>
<td>57.2 (1.40)%</td>
<td>53.6 (3.33)%</td>
</tr>
<tr>
<td>(17.5-22.8)</td>
<td>(55.2-58.3)</td>
<td>(49.0-56.9)</td>
<td></td>
</tr>
<tr>
<td>5 seconds</td>
<td>12.3 (0.58)%</td>
<td>55.2 (1.49)%</td>
<td>49.9 (1.86)%</td>
</tr>
<tr>
<td>(11.7-13.1)</td>
<td>(55.3-56.9)</td>
<td>(48.2-52.5)</td>
<td></td>
</tr>
<tr>
<td>20 seconds</td>
<td>1.6 (1.01)%</td>
<td>53.7 (1.10)%</td>
<td>49.8 (2.33)%</td>
</tr>
<tr>
<td>(7.8-10.1)</td>
<td>(52.1-54.7)</td>
<td>(47.2-52.8)</td>
<td></td>
</tr>
<tr>
<td>Multiple puffs (flow 60 l/min)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 puffs</td>
<td>16.3 (1.55)%</td>
<td>53.4 (1.40)%</td>
<td>48.8 (1.63)%</td>
</tr>
<tr>
<td>(14.1-18.4)</td>
<td>(51.5-54.9)</td>
<td>(46.6-50.4)</td>
<td></td>
</tr>
<tr>
<td>5 puffs</td>
<td>11.2 (1.24)%</td>
<td>53.3 (1.30)%</td>
<td>48.6 (1.52)%</td>
</tr>
<tr>
<td>(10.4-13.2)</td>
<td>(51.9-54.9)</td>
<td>(46.6-50.3)</td>
<td></td>
</tr>
</tbody>
</table>

Babyhaler, 1160 μg (1070–1208 μg) for the reduced static Babyhaler, 1133 μg (1086–1212 μg) for the static Babyspacer, 1043 μg (979–1098 μg) for the reduced static Babyspacer, 1047 μg (1032–1063 μg) for the static Aerochamber, 1014 μg (960–1078 μg) for the reduced static Babyspacer, 991 μg (980–1023 μg) for the static Nebuhaler, 1074 μg (994–1150 μg) for the reduced static Nebuhaler, and 1050 μg (1015–1075 μg) for the Nebuchamber.

Table 1 shows the amount of particles of <6.8 μm delivered to stages 3 and 4 as a percentage of the total actuated dose for the different spacers at static and reduced static conditions. There was no significant difference in drug delivery from different static plastic spacers. The Nebuchamber had a higher delivery (p<0.001) than all static plastic spacers (fig 1). However, compared with reduced static plastic spacers, this effect was reduced or eliminated. The reduced static Nebuhaler had a higher delivery than all reduced static small volume plastic spacers (p<0.001) and the Nebuchamber (p<0.001). The reduced static Babyhaler had a higher delivery than the reduced static Babyspacer (p<0.001), the reduced static Aerochamber (p<0.001), and the Nebuchamber (p<0.05).

Table 2 shows the amounts of particles of <9.6 μm for flow rates of 10 l/min and 30 l/min and particles of <6.8 μm for a flow rate of 60 l/min delivered to stages 3 and 4 as a percentage of the total actuated dose for the static and reduced static Babyhaler and the Nebuchamber.

Drug delivery at a flow rate of 30 l/min was similar to that at 10 l/min for the reduced static Babyhaler and the Nebuchamber. However, drug delivery at 30 l/min was higher (p<0.05) than at 10 l/min for the static Babyhaler (fig 2).

Delay resulted in lower drug delivery in the static Babyhaler (fig 3). The decrease in delivery of particles of <6.8 μm for a delay of one second was 13.4% of the total amount (p<0.001) compared with 20.6% (p<0.001) for a delay of five seconds and 24.3% (p<0.001) for a 20 second delay. Delay had no significant effect on drug delivery with the reduced static Babyhaler and the Nebuchamber.

Multiple actuations also resulted in a significant decrease in drug delivery for the static Babyhaler (fig 4). The decrease in delivery of particles of <6.8 μm for two puffs was 16.6% (p<0.001) and for five puffs was 21.7% (p<0.001) of the total amount, respectively. Differences in drug delivery from the reduced static Babyhaler and the Nebuchamber for multiple actuations were less pronounced but still significant (p<0.05 and p<0.01, respectively).

Discussion

Electrostatic charge was the major influence on delivery of salbutamol generated by a pMDI from plastic spacers. In addition, low flow, delay, and multiple actuations resulted in decreased delivery from static spacers. Their effect was greatly reduced or even eliminated by reducing the charge, although multiple actuations still resulted in a significant decrease in delivery. For drug delivery from reduced static spacers the volume and the shape appear to be the most important factors.

The most likely explanation for these results is the increased residence time of the aerosol within the spacer with lower flow, increased...
delay, and multiple actuations. The amount of aerosol attracted to the spacer surface by the electrostatic charge depends on the time between actuation of the pMDI into the spacer and clearing of the spacer.

Our results can be of practical consequence. As charge is the major factor which decreases delivery, it is very important to avoid it. Recent studies have shown that charge is reduced on a plastic spacer by using an antistatic lining.\(^7\) This may not be a practical treatment for spacers used by patients. Conducting materials carry no electrostatic charge, so a spacer made of steel solves the problem of reduced drug delivery due to electrostatic charge.\(^8\) A recent study has shown that a metal spacer is superior to plastic spacers, even if electrostatic charge is reduced on the surface of a plastic spacer.\(^9\) However, the authors did not measure the electrostatic charge and therefore did not prove that priming a plastic spacer with multiple actuations before use effectively reduces the charge. In contrast, we have shown that the problem of electrostatic charge is solved by coating a plastic spacer with an ionic detergent for 24 hours. This procedure greatly reduced the electrostatic charge – probably by the build up of a conducting layer on the spacer surface. This effective and practical treatment improved delivery from plastic spacers.

Delivery from reduced static spacers was mostly dependent on the volume and the shape of the spacer. The actuated aerosol cloud is held more efficiently in a large volume spacer.\(^10\) A large volume spacer may therefore be superior to small volume spacers. Inhalation therapy in infants is characterised by absent compliance and coordination and by different breathing patterns from those of older children and adults. An optimal inhalation device and inhalation method are therefore even more important in infants. Small volume spacers can be cleared easily with smaller tidal volumes\(^8\) and have been shown to be useful for aerosol therapy in infants.\(^11\)

Inspiratory flow rates in infants are likely to be less than 10 l/min. Our results can therefore be directly applied to children over two years of age as their inspiratory flow rates are likely to be over 10 l/min. However, our finding that the delivery from static spacers is decreased with lower flow rates may suggest that the effect on delivery of flow rates of less than 10 l/min would be even greater.

Compliance and coordination problems in inhalation therapy in infancy may result in delays between actuation and inhalation and also in multiple actuations. These factors greatly influence the drug delivery from static spacers only. The use of a reduced static spacer may allow improved inhalation therapy in infants as the influences of low flow, delay, and multiple actuations are greatly reduced or even eliminated.

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