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Electrostatic charge on spacer devices and salbutamol response in young children

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Abstract

Electrostatic charge on plastic spacer devices may affect the efficacy of inhaled drugs, but its consequences have never been evaluated in asthmatic children with airflow limitation. At the end of a positive metacholine challenge, 64 children (51.3 ± 12.9 months, 32 boys, specific airway resistance (SRaw) 257.1 ± 56.7% and forced expiratory volume in 1 s (FEV_1) 64.2 ± 17.9% of the predicted value) inhaled one puff of hydrofluoroalkane-134a (HFA-134a) salbutamol (Ventoline®), and 15 min later two other puffs (total dose of 300 μg), delivered through either a new static Babyhaler® ($n = 21$), a detergent-coated, reduced static, Babyhaler® ($n = 20$), or a metal NES-Spacer® ($n = 23$) equipped with facemask. SRaw and FEV_1 were measured after each treatment and compared between groups by a Kruskal–Wallis test. The first 100 μg salbutamol induced a 151.7 ± 43.9% decrease in SRaw and a 19.9 ± 10.6% increase in FEV_1. Additional 200 μg salbutamol allowed a supplementary decrease of 35.1 ± 25.7% in SRaw and increase of 12.1 ± 11.8% in FEV_1, without significant difference between the spacer devices. Electrostatic charge on spacer devices does not affect bronchodilation with HFA-134a salbutamol in metacholine-challenged pre-school children. This could be in part explained by the use of supramaximal doses of salbutamol.

Keywords: Asthma; Children; Electrostatic charge; Salbutamol; Spacer devices

1. Introduction

Pressurised metered-dose inhalers (pMDIs) attached to spacer devices are widely used for delivering anti-asthma medications and, in pre-school children, are even considered as the best method of inhaled treatments delivery (O'Callaghan, 1997; Warner and Naspitz, 1998). However, drug delivery from spacer devices may be affected by various factors, such as spacer volume, type of valve, dead space between inlet and outlet valve, electrostatic charge, spacer emptying pattern, mode of inhalation breathing, and the drug–spacer combination (Bisgaard, 1999; Dolovich, 1999; O'Callaghan and Barry, 2000; Dubus et al., 2001).

Electrostatic charge is inherent to the non-conducting surface of plastic spacer devices. The higher the electrostatic charge is, the higher is the amount of aerosolised drug attracted to the wall of the plastic spacer device, and, thus, retained within the spacer device (O'Callaghan et al., 1993). In vitro studies, all demonstrate that the drug output from an electrostatically charged spacer device is considerably decreased when compared with an electrostatically reduced or a metal non-electrostatic spacer device

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(Bisgaard, 1995; Dewsbury et al., 1996; Wildhaber et al., 1996a,b; Barry and O'Callaghan, 1997; Berg et al., 1998). Moreover, electrostatic charge increases the variability of dose delivery (Janssens et al., 1999; Wildhaber et al., 2000a,b). Scintigraphic studies with labelled salbutamol and budesonide show that the reduction in the electrostatic charge of the plastic spacer devices induces a 10–35% increase in lung deposition in children and adults with asthma (Kenyon et al., 1998; Piérart et al., 1999; Wildhaber et al., 2000a,b). Two pharmacokinetic studies demonstrate that the electrostatic charge in plastic spacers decreases the delivery of salbutamol to the lungs with an approximate twofold reduction in lung bioavailability either with Volumatic® (Glaxo-SmithKline, Paris, France) in adults (Clark and Lipworth, 1996) and Babyhaler® (Glaxo-SmithKline) in children (Anhoj et al., 1999). A recent pharmacodynamic study, conducted in 20 volunteers adults with a bronchodilator responsive airflow limitation, shows that a 10% increase in pulmonary function is obtained with less salbutamol when using treated rather than untreated Volumatic® (Wildhaber et al., 2000a,b). Conversely, in a crossover study conducted in 90 young children with stable asthma, the change in peak expiratory flows measured after inhalation of HFA-salbutamol from the non-static NES-Spacer® (AstraZeneca, Nanterre, France) compared with static plastic spacer devices or the same plastic spacer devices treated to eliminate static charge are the same (Dompeling et al., 2001). Therefore, such results might be different in asthmatic children with bronchial obstruction.

This study was undertaken to assess whether the use of small volume spacer devices with different electrostatic charge affected the bronchodilator response of cumulative doses of hydrofluoroalkane-134a (HFA-134a) salbutamol on the recovery from metacholine-induced bronchoconstriction in pre-school children with asthma.

2. Material and methods

2.1. Patients

Children between ages 3 and 6 years with a clinical diagnosis of asthma (Warner and Naspitz, 1998) and a positive metacholine challenge were recruited from December 1999 to December 2000. These children had been sent to the Laboratory by their paediatrician or pulmonologist to perform pulmonary function tests (PFTs) with a metacholine challenge. Over 1 year, 87 children were tested. Among them, 2 were unable to perform PFTs, 21 had a negative metacholine challenge, and 64 met the inclusion criteria. When satisfying the criteria, children were asked to participate to the bronchodilator challenge. Data on asthma were obtained by delivering a questionnaire to the parents. This study was approved by the local ethics committee and informed written consent was obtained from all the families.

2.2. Metacholine challenge

All baseline PFTs were performed between 09:30 and 12:00 h. Parents were instructed to withhold any kind of anti-asthmatic, anti-histamine or inhaled therapy for 24 h before the tests. Children with a concomitant upper airway infection or asthma exacerbation, which could have influenced the PFTs, were excluded. The PFTs consisted of a flow volume spirometric test and SRaw measurements with a constant body plethysmograph (model Master Lab Jaeger, Wurzburg, Germany), using a method that we have previously described in such young children (Badier et al., 1999). The mean of five reproducible measurements was used each time. To improve reproducibility, we used a computer game where children had to blow four candles on the screen of the computer. The functional measurements were compared with the predictive values of Zapletal (Zapletal et al., 1987).

Metacholine challenge was performed only if a normal baseline test was obtained, i.e. a value of specific airway resistance (SRaw) $\leq$120% of the predicted value and a value of forced expiratory volume in 1 s (FEV_1) $\geq$80% of the predicted value. For metacholine inhalation, a standardised dosimeter technique was used. Metacholine puffs were delivered by a dosimeter (MEFAR dosimeter, Electromedicalli, Brescia, Italy): air driving pressure = 1.65 kg/cm^2; air flow rate = 70–75 l/min; particle size = 0.5–4 μm. Two parameters were adjusted before the test: a nebulisation time of 1.2 s and a pause time of 5 s between two puffs. A metacholine solution of 2 mg/ml was used and 3 ml of the solution was placed in the nebuliser (20 μg of metacholine delivered per puff). Cumulative doses of

metacholine (40, 60, 100, 100 μg and a further 100 μg if necessary in order to reach the maximal dose of 400 μg) were administered. SRaw and FEV_1 measurements were performed 2 or 3 min after each inhaled dose of metacholine. Because of the well known difficult reproducibility of spirometric measurements in the pre-school children, the metacholine challenge was considered positive when a twofold increase of SRaw was obtained. The concentration of metacholine which produced this twofold increase of SRaw, or provocative dose, was noted.

2.3. Salbutamol challenge

When the metacholine challenge was positive, we administered one puff, followed 15 min later by two individual puffs, of HFA-134a salbutamol pMDI (Ventoline®, Glaxo-SmithKline; one puff = 120 μg salbutamol sulphate = 100 μg salbutamol base) through one of the following spacer devices equipped with its own facemask: a brand new electrostatically charged 350 ml Babyhaler® which had been stored in its original plastic bag, an electrostatically reduced 350 ml Babyhaler®, and a metal non-electrostatic 250 ml NES-Spacer® (also called Nebuchamber®). The method used to reduce the electrostatic charge on Babyhaler® consisted of soaking the spacer for a few minutes in a detergent solution (Palmolive®, 1:5000 dilution) and to allow it to drip-dry for 12–24 h before use (Piérart et al., 1999). Each spacer device was new before use. Spacer devices were used in a random order. The salbutamol pMDI was vigorously shaken and primed by firing two puffs in the room. The child was instructed to breath quietly into the spacer device via the face mask. Then, one puff was delivered into the spacer device and inhaled in five quiet respiratory cycles allowing the valves to move. SRaw and FEV_1 measurements were performed 15 min after the inhalation. Then, two other individual puffs of Ventoline® were administered in the same conditions than previously described and followed by a last PFT 15 min later. Pulsed oxymetry and heart beat were recorded during all the procedure.

2.4. Statistical analysis

The results were expressed as means (±S.D.) and compared between the three groups by a Kruskal–Wallis non-parametric ANOVA. The bronchodilator response was measured as a difference between pre-treatment and post-treatment values of SRaw and FEV_1, and was expressed in percent of the predicted value (Waalkens et al., 1993; Chrystyn, 1994). $\Delta_{100\,\mu g}$SRaw and $\Delta_{100\,\mu g}FEV_1$ represented the difference between the post-metacholine value of the respective spirometric indices and the value obtained after the inhalation of 100 μg salbutamol. $\Delta_{200\,\mu g}$SRaw and $\Delta_{200\,\mu g}FEV_1$ represented the difference between the post-100 μg salbutamol value of the respective spirometric indices and the value obtained after the inhalation of 200 μg salbutamol. $\Delta_{300\,\mu g}$SRaw and $\Delta_{300\,\mu g}FEV_1$ represented the difference between the post-metacholine value of the respective spirometric indices and the value obtained after the inhalation of the total dose of salbutamol, i.e. 300 μg. A P value <0.05 was considered significant.

3. Results

No metacholine-challenged child refused to participate to the study and all children achieved successfully the bronchodilator protocol. Tolerance was excellent and no side effect was noted. The main characteristics of the 64 children are presented in Table 1. Their mean age was 51.3 ± 12.9 months. There was 32 boys (50%). The mean standing height was 103.0 ± 8.4 cm and the mean weight was 16.8 ± 3.9 kg, without significant difference between the three groups. The children were in majority (59.4%), treated with long-term inhaled steroids administered through a spacer device. No long-term bronchodilator treatment was prescribed. The values of baseline PFTs were in the normal range for all children. The provocative dose of metacholine for doubling SRaw was higher in the NES-Spacer® group than in the two others but without significant statistical difference. The level of metacholine-induced bronchoconstriction was similar in the different groups.

Results of the salbutamol challenge are reported in Table 2 concerning the SRaw values and in Table 3 concerning FEV_1 values. No difference was noted at any dose of salbutamol between the three groups for the spirometric values. One puff of Ventoline® (100 μg salbutamol) allowed a mean 151.7 ± 43.9% decrease in SRaw and a mean 19.9 ± 10.6% increase in FEV_1.

Table 1
Characteristics of the asthmatic children with results expressed as mean ± S.D.

	Children inhaling from a brand new Babyhaler® ($n = 21$)	Children inhaling from a detergent-coated Babyhaler® ($n = 20$)	Children inhaling from a metallic NES-Spacer® ($n = 23$)
Age (months)	51.4 (13.9)	51.6 (11.6)	50.9 (13.7)
Proportion of boys	$n = 12$ (57.1%)	$n = 10$ (50%)	$n = 10$ (43.5%)
Positive prick-tests	$n = 10$ (47.6%)	$n = 10$ (25.0%)	$n = 8$ (34.8%)
Inhaled corticosteroids	$n = 13$ (61.9%)	$n = 11$ (55.0%)	$n = 14$ (60.9%)
Baseline SRaw[a] (% predicted)	80.7 ± 22.1	85.5 ± 21.8	79.4 ± 17.8
Baseline FEV_1[b] (% predicted)	105.6 ± 10.9	101.3 ± 15.7	104.9 ± 13.5
Provocative dose (μg)	206.7 ± 117.2	207.1 ± 120.2	256.9 ± 102.8

[a] SRaw: specific airway resistance.
[b] FEV_1: forced expiratory volume in 1 s.

Table 2
Improvement in SRaw[a] in asthmatic children receiving one puff and then two puffs of HFA-134a salbutamol (total dose of 300 μg) via three different electrostatically charged spacer devices (results are expressed as mean ± S.D. and compared by a Kruskal–Wallis test)

	Children inhaling from a brand new Babyhaler® ($n = 21$)	Children inhaling from a detergent-coated Babyhaler® ($n = 20$)	Children inhaling from a metallic NES-Spacer® ($n = 23$)	P value
SRaw values (% predicted)				
Post-metacholine SRaw	262.8 ± 58.9	264.5 ± 64.3	244.0 ± 46.9	0.59
Post-100 μg salbutamol SRaw	115.1 ± 40.4	106.6 ± 28.3	94.4 ± 29.7	0.09
Post-300 μg salbutamol SRaw	76.2 ± 22.2	66.1 ± 14.4	66.3 ± 13.9	0.17
Differences (% predicted)				
$\Delta_{100\,\mu g}$SRaw[b]	−148.0 ± 43.3	−157.9 ± 50.0	−149.6 ± 40.0	0.80
$\Delta_{200\,\mu g}$SRaw[c]	−37.9 ± 29.4	−40.5 ± 20.2	−28.1 ± 26.0	0.16
$\Delta_{300\,\mu g}$SRaw[d]	−186.6 ± 53.9	−198.4 ± 56.4	−177.7 ± 39.0	0.54

[a] SRaw: specific airway resistance.
[b] $\Delta_{100\,\mu g}$SRaw: difference between post-100 μg salbutamol SRaw and post-metacholine SRaw.
[c] $\Delta_{200\,\mu g}$SRaw: difference between post-300 μg salbutamol SRaw and post-100 μg salbutamol SRaw.
[d] $\Delta_{300\,\mu g}$SRaw: difference between post-300 μg salbutamol SRaw and post-metacholine SRaw.

Table 3
Improvement in FEV_1[a] in asthmatic children receiving one puff and then two puffs of HFA-134a salbutamol (total dose of 300 μg) via three different electrostatically charged spacer devices (results are expressed as mean ± S.D. and compared by a Kruskal–Wallis test)

	Children inhaling from a brand new Babyhaler® ($n = 21$)	Children inhaling from a detergent-coated Babyhaler® ($n = 20$)	Children inhaling from a metallic NES-Spacer® ($n = 23$)	P value
FEV_1 values (% predicted)				
Post-metacholine FEV_1	63.3 ± 20.5	61.5 ± 13.2	68.0 ± 20.1	0.47
Post-100μg salbutamol FEV_1	83.1 ± 18.2	84.3 ± 16.9	86.2 ± 17.8	0.78
Post-300μg salbutamol FEV_1	94.4 ± 13.9	95.0 ± 14.5	99.7 ± 11.2	0.43
Differences (% predicted)				
$\Delta_{100\,\mu g}FEV_1$[b]	18.9 ± 12.0	22.8 ± 9.8	18.2 ± 9.9	0.31
$\Delta_{200\,\mu g}FEV_1$[c]	12.0 ± 11.2	10.7 ± 14.1	13.4 ± 10.8	0.47
$\Delta_{300\,\mu g}FEV_1$[d]	31.1 ± 15.8	33.5 ± 10.5	31.7 ± 13.4	0.83

[a] FEV_1: forced expiratory volume in 1 s.
[b] $\Delta_{100\,\mu g}FEV_1$: difference between post-100 μg salbutamol FEV_1 and post-metacholine FEV_1.
[c] $\Delta_{200\,\mu g}FEV_1$: difference between post-300 μg salbutamol FEV_1 and post-100 μg salbutamol FEV_1.
[d] $\Delta_{300\,\mu g}FEV_1$: difference between post-300 μg salbutamol FEV_1 and post-metacholine FEV_1.

The inhalation of two other puffs induced a supplementary decrease of 35.1 ± 25.7% in SRaw and a supplementary increase of 12.1 ± 11.8% in FEV_1. At the end of the bronchodilator challenge, all children recovered SRaw values less than 120% and/or FEV_1 values greater than 80% of the predicted values. Fifty-five children (85.9%) had spirometric values higher than their baseline values at the end of the study.

4. Discussion

In this pharmacodynamic study, we show in a group of 64 children, aged 3–6 years, with moderate provoked bronchial obstruction assessed either by SRaw or FEV_1 measurements, that there is no difference in bronchodilator response between a static plastic, a reduced static plastic and a metal spacer device.

Various techniques have been described to reduce the electrostatic charge on plastic spacers: by wiping the plastic spacer device with an anti-static cloth, by coating the inner walls with an anti-static lining, by priming the spacer device by firing placebo or drug doses so that the inner surfaces are coated with surfactant, or by washing the spacer device with water or a detergent solution (O'Callaghan et al., 1993; Clark and Lipworth, 1996; Dewsbury et al., 1996; Wildhaber et al., 1996a,b, 2000a,b; Barry and O'Callaghan, 1997; Berg et al., 1998; Kenyon et al., 1998; Piérart et al., 1999; Janssens et al., 1999). Using the same protocol that we used, Piérart (Piérart et al., 1999) found that the electrostatic charge was negligible on the surface of all detergent-coated spacer devices (less than 1.2 $\mu C/m^2$, with C = Coulomb), regardless of the brand of detergent or the dilution used, and high on all non-coated spacer devices (greater than 5 $\mu C/m^2$). The mean lung deposition of five individual puffs (500 μg) of labelled chlorofluorocarbon (CFC) salbutamol in healthy adults was 11.5% when using a static spacer device compared to 45.6% when using a detergent-coated spacer device ($P < 0.001$). In another study, the variability of the amount of salbutamol deposited in untreated spacer devices was also higher when compared to non-static spacer devices, with a coefficient of variation of 21% versus 13% (Wildhaber et al., 2000a).

We found that the pharmacodynamic effect of 100 μg, and then of a total of 300 μg, HFA-134a salbutamol was similar between the groups whatever the electrostatic charge on spacer devices. We studied HFA-134a salbutamol in spite of everything because HFA is going to replace CFC in all pMDIs and because only HFA-134a Ventoline® is currently used in our country. Salbutamol was delivered from the Babyhaler®, but also from the NES-Spacer®, despite the fact that pMDI did not fit well in the metal spacer device, because in our experience a lot of patients use this combination of drug and spacer device.

Our results are in accordance with those obtained in children with stable asthma, where the mean difference of the change in peak expiratory flow between small non-electrostatic (NES-Spacer®) and large (Volumatic®) or small (Aerochamber®, Boehringer Ingelheim, Alkmaar, the Netherlands) electrostatic spacer devices was only +1.7% (−1.3 to 4.7%) after 100 μg HFA-134a salbutamol and +1.9% (−1.4 to 5.1%) after 400 μg HFA-134a salbutamol (Dompeling et al., 2001). However, a recent pharmacokinetic study conducted in five healthy children demonstrated that the inhalation of four single puffs of HFA-134a salbutamol (400 μg) through a new Babyhaler® or a new Aerochamber® induced a twofold decrease in both peak and average plasma salbutamol levels compared to the inhalation through a Babyhaler® coated with benzalkonium chloride (Anhoj et al., 1999).

Failure to identify significant in vivo differences between spacer devices with different electrostatic charge may have at least two causes. The first one is that we used supramaximal doses of salbutamol and that children who were challenged by metacholine were near their plateau with 100 μg HFA-134a salbutamol, even delivered from a statically charged Babyhaler®. Consequently, differences found in in vitro, scintigraphic, and pharmacokinetic studies may be clinically irrelevant because of the optimal bronchodilation obtained with only 100 μg salbutamol. The two pharmacodynamic studies conducted in children with asthma, i.e. that of Dompeling (Dompeling et al., 2001) and ours, support this hypothesis. The time course of bronchodilation may have also contribute to our apparent dose–response effect and be the explanation for the further bronchodilation seen after the second and third puff. The second possible cause is that the proposed benefits of anti-static devices are nullified by the inherent variability of salbutamol delivery from spacer devices due to breathing patterns of the children, handling of spacer devices, etc.

(Dewsbury et al., 1996; Janssens et al., 1999) and/or by the important amount of salbutamol available for inhalation because of the specific aerodynamic behaviour of HFA aerosol with spacer devices (Barry and O'Callaghan, 1997; Dubus et al., 2001). However, metacholine challenge does not mimic an acute asthma attack and our results might be different in "natural" and more severe bronchoconstriction.

In conclusion, this study demonstrates that the inhalation of HFA-134a salbutamol through differently electrostatically charged small volume spacer devices equipped with face masks induces a similar bronchodilation in asthmatic pre-school children with a metacholine-induced bronchoconstriction. Our findings only concern HFA-134a salbutamol, small volume spacer devices, and metacholine-challenged pre-school children.

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