Drug Delivery in Asthmatic Children Following Coordinated and Uncoordinated Inhalation Maneuvers: A Randomized Crossover Trial

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Abstract

Background: Valved holding chambers (VHCs) are used in children to deliver pressurized metered dose inhalers (pMDI). *In vitro* data suggest that uncoordinated use decreases the amount of drug available for inhalation. We hypothesize that in an *ex vivo* study, the coordinated maneuver will deliver more drug than the uncoordinated one.

Patients and Methods: Thirty-two clinically stable asthmatic children, ages 5–8 years, completed the study. An aerosol filter was interposed between a small-volume nonelectrostatic VHC and a mouthpiece to capture the drug emitted by one puff of Flovent[®] 220 mcg during tidal breathing. Inhalation and actuation parameters were measured by an electronic monitor, and the number of breaths required to empty the VHC was calculated. Subjects completed three coordinated and three uncoordinated (actuation at the beginning of inhalation and exhalation, respectively) runs in random order. Drug content from the filter and VHC was measured by high-performance liquid chromatography and expressed as percentage of emitted dose.

Results: [mean (99% confidence interval)] Filter dose was higher during coordinated technique 46% (43%–50%) than during uncoordinated technique 41% (37%–44%) ($p < 0.001$). Peak inspiratory flow and tidal volume were 23.2 L/min (21.3–25.1 L/min) and 281 mL (251–311 mL), respectively. Subjects required three breaths to empty the VHC in 96% of the tests.

Conclusions: Actuating the pMDI into a small-volume nonelectrostatic VHC during exhalation reduced by 11% the amount of fluticasone captured at the exit of the VHC. Asthmatic children (5–8 years old) need three or less breaths to empty the small-volume VHC (NCT01714063).

Keywords: asthma, breathing pattern, fluticasone propionate, inhalation technique, valved holding chamber

Introduction

ASTHMA IS THE MOST COMMON CHRONIC ILLNESS in childhood affecting ~15% of the population. Inhaled corticosteroids are the cornerstone of the treatment of asthma and have been shown to be clinically safe in low and moderate doses.⁽¹⁾

The pressurized metered dose inhaler (pMDI) is used with a valved holding chamber (VHC) in pediatric patients.

Electrostatic charge of the plastic material used in some VHCs has been shown to reduce the amount of aerosol delivered. New VHCs are therefore mainly built of antistatic plastic materials that eliminate electrostatic charge.^(2–5) Caregivers and patients are instructed to breathe immediately after they actuate the pMDI.⁽⁵⁾ Improper inhalation technique has been associated to poor asthma stability.⁽⁶⁾ *In vitro* studies showed a decrease in drug output associated to actuation of the pMDI during exhalation.⁽⁷⁾ Therefore,

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knowing the variation of inhaled dose resulting from proper or improper technique is clinically relevant.

The amount of aerosol delivered through different pMDI-VHC combinations can be determined in both *in vitro* and *ex vivo* filter studies.^(8,9) In an *ex vivo* filter study, the subject uses the pMDI-VHC combination as per the manufacturer's instructions, but the drug is deposited onto a filter interposed between the VHC mouthpiece and the subject's mouth.⁽⁸⁾ The amount of drug deposited on the filter represents the amount of drug available for inhalation.

The objective of this study was to compare the amount of fluticasone propionate (fluticasone) delivered via pMDI-VHC combination in asthmatic children 5–8 years old, when using a coordinated or an uncoordinated technique. We hypothesized that using a coordinated technique would significantly increase drug delivery.

Patients and Methods

The study was performed at Arkansas Children's Hospital; it was approved by the University of Arkansas Institutional Review Board (# 137456) and was registered at clinicaltrials.gov (NCT01714063). Parents provided written consent and subjects 7 years or older provided written assent. All the study-related procedures were done by the principal investigator (A.B.).

The inclusion criteria were (1) age 5–8 years followed at Arkansas Children's Hospital, (2) asthma diagnosis, clinically stable at time of enrollment, (3) prescribed an inhaled corticosteroid via pMDI-VHC combination, (4) previously used a VHC with mouthpiece or be able to use it, and 5) able to complete the study protocol.

The exclusion criteria were (1) inability to understand instructions, (2) participation in other clinical trials in the past 4 weeks, and (3) history of clinically significant respiratory disease during the 4 weeks before the study.

The study was designed as randomized, single-blind, crossover trial with parents and subjects unaware of the timing of the actuation of the pMDI. The study consisted of a single session without follow-up. The study was designed to recruit up to 40 subjects with the goal of having 16 subjects who completed the study in each of the age groups: 5–6.5 years (group 1) and 6.6–8 years (group 2). The following information was recorded: age, height, weight, gender, ethnicity, and number of years using VHC and mouthpiece. A CONSORT flowchart can be found in Figure 1.

The pMDI used was fluticasone (Flovent HFA 220 μg /actuation; GSK, Research Triangle Park, NC). The VHC used was OptiChamber Diamond (Respironics Respiratory Drug Delivery Limited UK, Chichester, United Kingdom).⁽¹⁰⁾ The small volume (145 mL) VHC is made of transparent nonelectrostatic plastic material and has a low-resistance inspiratory valve within the mouthpiece, and a low-resistance expiratory valve placed on top of the mouthpiece assembly (Fig. 2). The plastic boot of the pMDI was modified to allow the connection of a data logger developed by Respironics (Fig. 3).⁽¹¹⁾ The data logger had an accelerometer to detect the shaking of the pMDI, an ultrasonic detector to monitor the actuation of the pMDI, and a flow sensor to record the subject's inhalation profile (Fig. 3). The sensors were wired to an electronics enclosure where the signals were converted for communication to a personal computer.⁽¹¹⁾

The study comprised eight measurements and each used a new VHC and filter. The first and the last measurements were carried out for quality control purposes using a vacuum source and did not involve the subject. Measurements 2 to 7 comprised three coordinated and three uncoordinated maneuvers with the subject. During coordinated and uncoordinated maneuvers, the investigator actuated the pMDI at the beginning of the inhalation and at the beginning of the exhalation, respectively. The order of these maneuvers was predetermined by a computer-generated randomization in block.

A new pMDI of fluticasone was used with each subject and was primed with four actuations to waste. A VHC was connected to a low dead space filter holder with a disposable filter media (Filtrete G-200; 3M, St. Paul, MN). The filter captures 99.3% of the fluticasone aerosol that is delivered to it, therefore minimizing subject exposure. At the beginning of the test, a volume calibration and sensor verification of the data logger were performed. The filter holder-VHC-pMDI was connected to a suction pump (30 L/min) and was actuated 10 times allowing 5 seconds of shaking before actuation and 30 seconds of interval between actuations.

Next, a new mouthpiece-filter-VHC was connected to the pMDI with data logger through the posterior opening of the VHC. The pMDI was then shaken and the subject was instructed to put the mouthpiece in his/her mouth, create a seal with his/her lips, and breathe tidally. The investigator monitored the subject's chest movement and the closing of the exhalation valve to determine the respiratory time (inhalation vs. exhalation). The investigator actuated the pMDI either in a coordinated or uncoordinated maneuver according to the randomization schedule and the subject was instructed to perform three tidal breaths. Five more tests were carried out with each subject and the second quality control measurement test was carried out. Samples were individually packaged and shipped to the Respironics laboratory in the United Kingdom, where drug analysis was performed using a validated high-pressure liquid chromatography method according to industry standards. The laboratory was blinded to all trial information.

The principal investigator (A.B.) kept the sponsor blinded to the identity of the subjects and once the data logger analysis and the biochemical analysis were completed, he provided the key to connect both data sets. The primary outcome was the amount of fluticasone captured in the filter (filter dose). Under current regulations, pMDIs are allowed to deliver a range between 85% and 115% of the nominal dose.⁽¹²⁾ Therefore, differences smaller than 15% are unlikely to be clinically meaningful. In an attempt to normalize the data, we expressed the amount of fluticasone captured in the filter as the percentage of the delivered drug (filter + VHC). Raw data from the data logger were processed to remove noise from the signal. Peak inspiratory flow and tidal volume for the three breaths that occurred after the actuation were determined and the number of breaths required to empty the VHC were calculated.⁽¹¹⁾ Figure 4 shows an example of the data logger output for a coordinated and uncoordinated maneuver. All these variables were reported as mean and 99% confidence interval (CI).

We used a paired *T*-test for statistical analysis to compare the filter dose. Using the 1% significance level and assuming a between-subject standard deviation of 60 μg (27%) for the difference between coordinated and uncoordinated filter

FIG. 1. CONSORT flowchart.

FIG. 2. Optichamber diamond.

does, 32 subjects are sufficient to detect a $45 \mu\text{g}$ (20%) difference with 95% confidence. Grub's test with a significance level <0.01 was used to detect the presence of outliers. We used unpaired T -test to compare baseline characteristics between the two age groups. The Mann-Whitney test was used to compare the number of years the subjects used a VHC. Chi-square statistics was used to compare the proportion of subjects that was Caucasian and the proportion of subjects with mouthpiece experience. The significance level was established at 0.05.

Results

Subject flow

Subjects were recruited between September 26, 2013, and May 1, 2014. A subject flow chart can be seen in Figure 1.

FIG. 3. Investigational setup with pressurized metered dose inhaler (pMDI) Data logger.

Subjects in group 1 were younger, and had less experience using a mouthpiece than subjects in group 2 (Table 1). However, all the subjects had minimal experience presenting a median (95% CI) of 0 (0–0.5) years of mouthpiece experience.

Filter data

The mean (99% CI) filter dose was higher during coordinated technique 46% (43%–50%) than during uncoordinated technique 41% (37%–44%) ($p < 0.001$) (Fig. 5). The difference remained statistically significant for both the older 45% (39%–51%) versus 40% (35%–45%) for coordinated and uncoordinated techniques, respectively, $p < 0.001$ and the younger groups 48% (44%–52%) versus 41% (36%–47%) for coordinated and uncoordinated techniques, respectively, $p < 0.001$.

Breathing profile data

Breathing profiles were similar among the three breaths that occurred after the actuation of the pMDI ($p = 0.65$ and $p = 0.05$ for peak inspiratory flow during coordinated and uncoordinated maneuvers; and $p = 0.94$ and $p = 0.78$ for tidal volume during coordinated and uncoordinated maneuvers) (Table 2). Both peak inspiratory flow and tidal volume were similar between coordinated and uncoordinated maneuvers. This was true for when either the three breaths that occurred after the actuation of the pMDI ($p = 0.05$ and $p = 0.09$ for inspiratory peak flow and tidal volume, respectively) or the first breath only was analyzed ($p = 0.16$ and $p = 0.81$ for inspiratory peak flow and tidal volume, respectively).

The mean (99% CI) peak inspiratory flow and tidal volume for all subjects were 23.2 L/min (21.3–25.1 L/min) and 281 mL (251–311 mL), respectively.

The subjects required three, two, or one breath to empty the VHC in 96% (163/170), 93% (158/170), and 83% (141/170) of the maneuvers, respectively.

No adverse events occurred during the trial.

Discussion

Asthmatic children aged 5–8 years, with little mouthpiece experience, showed a statistically but unlikely to be clinically significant difference in the percentage of emitted dose of fluticasone captured in a filter, located at the exit of a VHC, between coordinated and uncoordinated inhalation maneuvers when using a small-volume, nonelectrostatic VHC with tidal breathing inhalation. The volume of the VHC was emptied by almost all subjects in three breaths or less.

The negative impact on the amount of drug available for inhalation resulting from actuating the pMDI at the beginning of the exhalation was smaller than expected. Foss and Keppel reported a 46% decrease in drug output from a small-volume VHC when the inhalation technique was changed from coordinated to uncoordinated.⁽⁷⁾ The difference could be explained, in part, by the fact that the VHC used in this study was made of a nonelectrostatic material, but that used by Foss was not.^(2–4) This is consistent with the findings of Pierart et al. who reported a 3.9-fold difference in intrapulmonary deposition of a radiolabeled aerosol when the electrostatic charge of a spacer was reduced by prewashing it with household detergent.⁽⁴⁾

The same group showed in an *in vitro* study, a 37.4% increase in drug output when the spacer was prewashed, thus reducing its electrostatic charge.⁽⁴⁾ Also, Wildhaber et al., in an *in vitro* study, showed that a delay between actuation and inhalation significantly reduced drug output in the untreated spacer but not in the one with reduced static charge.⁽¹³⁾ Although the reduction in filter dose that occurred between coordinated (46%)

FIG. 4. Output from Data logger for a coordinated and uncoordinated maneuver.

and uncoordinated (41%) maneuvers was statistically significant, it is unlikely to be clinically relevant.⁽¹²⁾

The recorded tidal volumes averaged 10–11 mL/kg, which is larger than typically expected for this age group. However, this is consistent with previous studies that show larger than ex-

pected tidal volumes during inhalation through VHCs.^(11,14) Nonetheless, the average tidal volume recorded in this study was smaller than in other studies (281 vs. 400 mL). The differences could be attributed to the fact that our population was older and therefore able to better follow instructions.

TABLE 1. DEMOGRAPHICS

	All	5–6.5 years	6.6–8 years	p
No. of subjects	32	16	16	0.99
Age, mean (SD), years	6.4 (0.8)	5.7 (0.4)	7.1 (0.4)	<0.0001
Male, <i>n</i> (%)	20 (63)	8 (50)	12 (75)	0.27
Caucasian, <i>n</i> (%)	17 (53)	10 (63)	7 (44)	0.49
Height, mean (SD), cm	119.3 (7.7)	115.1 (6.2)	123.4 (6.9)	0.001
Weight, mean (SD), kg	26.4 (8.6)	24.7 (8.8)	28 (8.4)	0.28
VHC experience, median (95% CI), years	3 (2.5–4)	3 (2.5–4)	3.5 (2–5)	0.93
Previous mouthpiece experience, <i>n</i> (%)	13 (41)	2 (13)	11 (69)	0.003

p-Values that are in bold font are statistically significant.

CI, confidence interval; VHC, valved holding chamber.

FIG. 5. Filter dose during coordinated and uncoordinated maneuvers.

The finding that two to three tidal breaths are sufficient to empty a small-volume VHC is consistent with the previous report by Schultz et al.⁽¹⁴⁾ In their study, they recorded the breathing pattern through a device of similar size and shape and then used the breathing patterns for *in vitro* evaluation. Our study incorporated a real-life factor by recording the tidal breathing pattern during the actual drug delivery with concomitant capture of drug available for oral inhalation (filter dose). The findings of both studies should be considered when planning future educational asthma activities.

Our findings have several important clinical implications. First, 5–8-year-old children with little to no experience of using a VHC with mouthpiece can successfully use it after minimal instruction. This is important because previous studies reported that the addition of dead space that occurs when a facemask is added to a VHC results in a decrease in

the amount of drug available for oral inhalation.⁽¹⁵⁾ Also, the use of a mouthpiece avoids any facial, and potentially ocular, exposure that occurs with a facemask.⁽¹⁶⁾ Traditionally, the use of mouthpiece has been associated with the performance of a single-breath inhalation maneuver. In our study, we successfully used tidal breathing (three breaths) following the actuation of the inhaler. Patients should be changed from the VHC/facemask to VHC/mouthpiece once they are able to seal their mouths around the mouthpiece even if they are still not able to perform a single inhalation maneuver.

Second, 5–8-year-old children require only two to three breaths to empty the VHC. A lower number of required breaths than previously suggested could potentially enhance adherence to therapy by reducing the treatment burden.

Finally, our data suggest that in the age group studied while using a small-volume nonelectrostatic VHC, OptiChamber

TABLE 2. BREATHING PROFILES OBTAINED DURING INHALATION OF A PRESSURIZED METERED DOSE INHALER THROUGH A VALVED HOLDING CHAMBER

	Breath	Coordinated maneuver	Uncoordinated maneuver
Peak inspiratory flow, L/min	First	25.2 (20.5–30)	22.8 (17.6–28.1)
Peak inspiratory flow, L/min	Second	23.3 (18.5–28.1)	22 (17.3–26.6)
Peak inspiratory flow, L/min	Third	23.2 (18.3–28)	22.5 (17.1–27.9)
Peak inspiratory flow, L/min	All	23.9 (21.3–26.5) ^a	22.4 (19.6–25.2) ^a
Peak inspiratory flow, L/min	All	23.2 (21.3–25.1)	
Tidal volume, mL	First	286 (209–363)	269 (212–362)
Tidal volume, mL	Second	281 (215–363)	259 (186–333)
Tidal volume, mL	Third	302 (227–378)	266 (201–331)
Tidal volume, mL	All	291 (250–332) &	271 (228–314) ^b
Tidal volume, mL	All	281 (251–311)	

Data are expressed as mean (99% CI).

^a $p=0.053$ between coordinated and uncoordinated maneuvers.

^b $p=0.09$ between coordinated and uncoordinated maneuvers.

Diamond, the use of uncoordinated inhalation maneuver should not have significant consequences on drug delivery that could translate in loss of control of their asthma. Practitioners should be aware that if in a real-life situation patients are not responding to the prescribed therapy, every effort should be made to assure that the patients have a correct inhalation technique.

The study has some limitations: first, we did not measure particle size of the fluticasone aerosol. Second, we measured the drug available for inhalation but not the amount actually inhaled by the subjects. Moreover, we did neither measure lung deposition nor pharmacokinetics of the inhaled. These methods require the use of radio-labeled aerosols and frequent blood draws making them difficult to complete in children. Third, these findings should be limited to the studied age group and to a situation of clinical stability. Finally, all inhalation maneuvers were supervised by the investigators, and therefore, the reported differences could clinically be significant under real-life conditions. Future studies should include younger and older children and should be studied during an asthma exacerbation and after they have recovered.

Conclusion

In summary, 5–8-year-old asthmatic children with minimal mouthpiece experience are able to effectively use a small-volume VHC made of nonelectrostatic material with mouthpiece and require two to three breaths to empty its volume. Under these conditions, the use of an uncoordinated inhalation technique leads to a small reduction in the amount of drug available for oral inhalation.

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Authors' Contributions

All authors approved the final manuscript as submitted. A.B. conceptualized and designed the study, performed all patient-related study procedures, carried out the initial data analysis, drafted the initial manuscript, and revised it. D.v.H. designed the study, developed the data logger, standard operating procedures for transporting and analyzing samples, carried out the initial data analysis, and critically reviewed the initial draft. R.H. designed the study, developed the standard operating procedures for transporting and analyzing samples, carried out the initial data analysis, and critically reviewed the initial draft. L.H. developed the standard operating procedures for transporting and analyzing samples, and critically reviewed the initial draft. K.N. designed the study and critically reviewed the initial draft.

Author Disclosure Statement

A.B. served as Principal Investigator in clinical trials sponsored by Vertex, AbbVie, Allergan, Genentech, Janssen, Gilead, Teva, Philips, Novartis, National Institutes of Health, and Therapeutic Development Network. A.B. is a Science Advisor to the Device Human Factors Subgroup of

the International Pharmaceutical Aerosol Consortium on Regulation and Science (IPAC-RS). The Pediatric Aerosol Research Laboratory at Arkansas Children's Hospital Research Institute was partially established and receives partial support from the George Endowment for Asthma. R.H. and L.H. are employees of Respiroics Respiratory Drug Delivery UK Limited, Chichester, United Kingdom. D.v.H. is an employee of Respiroics, Inc., a Philips Healthcare company, Murrysville, PA. K.N. was an employee of Respiroics, Inc., a Philips Healthcare company, Parsippany, NJ, during part of the study.

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