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ORIGINAL RESEARCH

Two vs four puffs of albuterol: does dose change bronchodilator response?

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Background: Reversible obstruction on spirometry may be used to diagnose asthma. As per 2005 American Thoracic Society (ATS) guidelines, our pulmonary center began using 360 µg (four puffs) of albuterol rather than 180 µg (two puffs) to determine reversibility on spirometry starting in 2009.

Hypothesis: We hypothesized that fewer patients would respond to two puffs of albuterol than four puffs during spirometric testing.

Methods: We retrospectively reviewed records from new asthmatics seen in Pediatric Pulmonary Clinic from March 2002 to April 2014 who performed reproducible spirometry. Patients were divided into two groups based on whether they had received two or four puffs of albuterol for bronchodilator assessment. A positive bronchodilator response was defined as an increase of ≥12% in forced expiratory volume in one second (FEV_1) or ≥25% in forced expiratory flow ($FEF_{25–75\%}$). Data were expressed as percentages and mean ± standard error of the mean values. Chi-squared test and Student's *t*-test were utilized.

Results: Data were collected for 240 patients; 115 patients received two puffs of albuterol and 125 patients received four puffs. There were no significant differences in baseline characteristics between the two groups. There were no differences following two puffs or four puffs in changes in FEV_1 (10.0±1.1% vs 10.5±1.1% predicted) or $FEF_{25–75\%}$ (30.2±2.9% vs 33.5±2.9% predicted). Moreover, there was no difference in ATS-defined bronchodilator response between the two groups.

Conclusion: Based on the mean change in FEV_1 and overall bronchodilator responsiveness, two puffs of albuterol were not inferior to four puffs in the determination of bronchodilator responsiveness in our pediatric asthmatic patients.

Keywords: asthma, reversible obstructive lung disease, pulmonary function testing

Introduction

Asthma is a common pediatric disease characterized by airflow obstruction, bronchial hyperresponsiveness, and airway inflammation. It is well appreciated that patients' perception of airflow obstruction is highly variable and that medical history and physical examination are not reliable means of characterizing the extent of lung impairment or of excluding other medical conditions.[1] Thus, objective assessments of pulmonary function are necessary. Spirometry, particularly forced expiratory volume in one second (FEV_1), is considered the gold standard for the evaluation of airway obstruction, and the presence of reversible obstruction on spirometry following short-acting bronchodilator administration may be used to assist in the diagnosis of asthma.[1]

Albuterol is the commonest drug used in bronchodilator assessments. For determining bronchodilator responsiveness in our center, we had routinely given patients the

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standard clinically used dose of albuterol (ie, 180 μg, two puffs).[2] However, in 2005, a joint task force of the American Thoracic Society (ATS) and the European Respiratory Society (ERS) recommended that 360 μg (four puffs) of albuterol be used in these assessments.[3] The rationale for this increase was not fully explained. Nevertheless, in response to the new guidelines, our pulmonary center began using 360 μg (four puffs) of albuterol rather than 180 μg (two puffs) of albuterol to determine reversibility on spirometry. This change in practice raised the question of whether pulmonary physicians would identify more patients with a significant bronchodilator response following four puffs of albuterol than two puffs. Based on the ATS/ERS recommendations and published dose–response curves to albuterol,[4] we hypothesized that fewer patients would respond to two puffs of albuterol than four puffs and, thus, that two puffs were inferior to four puffs of albuterol during spirometric testing.

Methods

This retrospective pre-/post-study design was conducted at Connecticut Children's Medical Center and involved new patients diagnosed with asthma seen at the Pediatric Pulmonary Clinic at Connecticut Children's Medical Center from March 2002 to April 2014. Patient's records were obtained as a convenience sample. Potential associated factors and outcomes of children receiving four puffs of albuterol for bronchodilator testing (cases) were compared with children receiving two puffs of albuterol (controls). This study was approved by Connecticut Children's Medical Center's Institutional Review Board, and informed consent was waived due to its retrospective nature. Patient data confidentiality was maintained by assigning an anonymous study identifier to each patient. There was no identifying patient information stored with the data.

Newly referred patients with asthma whose pre- and postalbuterol spirometry were reproducible based on ATS/ERS criteria and met ATS/ERS guidelines criteria for spirometry[3] were included in the study. Patients completed multiple spirometry attempts if needed (up to a maximum of eight trials). Patients who had an initial visit prior to November 2009 received two puffs of albuterol with spacer, and patients who had an initial visit in November 2009 or later received four puffs of albuterol with spacer. Patients were excluded if they had cystic fibrosis, bronchopulmonary dysplasia, congenital heart disease, abnormal airway clearance, and restrictive lung disease or did not meet the inclusion criteria for acceptable spirometry. Patients were divided into two groups based on whether they had received two puffs of albuterol or four puffs of albuterol during spirometry. Additional data collected for each patient included age, gender, ethnic group, current use of inhaled corticosteroids, other asthma medication use (ie, montelukast and long-acting β-adrenergic agonists), prebronchodilator forced vital capacity (FVC; %FVC), pre-FEV_1 (%FEV_1), pre-FEV_1/FVC, pre-forced expiratory flow ($FEF_{25–75\%}$; %$FEF_{25–75\%}$), postbronchodilator FVC (%FVC), post-FEV_1 (%FEV_1), post-FEV_1/FVC, post-$FEF_{25–75\%}$ (%$FEF_{25–75\%}$), change in FVC, change in FEV_1, and change in $FEF_{25–75\%}$ (following bronchodilator administration). All spirometry measurements were expressed as percentage predicted based on National Health and Nutrition Examination Survey or Morris Polgar predictive values (based on age, height, weight, and gender). As per ATS guidelines, a positive bronchodilator response was defined as an increase of ≥12% in FEV_1 and/or an increase of ≥25% in $FEF_{25–75\%}$.[5]

Statistical analysis

Data were analyzed using StatView 5.0.1 (SAS Institute Inc., Cary, NC, USA) and were expressed as percentages and as mean ± standard error of the mean values. Chi-squared test and Student's *t*-test were utilized. Sample size was based on our primary endpoint of change in FEV_1 with each dose of bronchodilator. Assuming an average SD of 10 in the percentage predicted change in FEV_1, review of 63 records in each group would allow us to detect an increase in FEV_1 of 5% predicted with four puffs of albuterol vs two puffs, with power 0.9 and alpha 0.05. We reviewed approximately twice this many records in case the estimates were too conservative and in order to allow for subgroup analyses. Secondary endpoints included differences in $FEF_{25–75\%}$ changes and proportions of identified bronchodilator responders in each group. When no differences were found in responses to two or four puffs of albuterol, we performed additional noninferiority testing of two puffs relative to four puffs, with regard to changes in FEV_1. We chose a noninferiority margin of 6% predicted FEV_1 change, half of what most authorities define as a meaningful bronchodilator response (ie, 12–15% increase)[5] and well within measurement variability (ie, increments <8%).[5]

Results

Data were collected from 240 patients: 115 patients received two puffs of albuterol and 125 patients received four puffs of albuterol. There were no significant adverse effects reported in either group, and also minor side effects were not recorded. Baseline characteristics are summarized in Table 1. The age of patients ranged from 5 to 17 years. The majority of patients were Caucasian, and there were more males than females in the study. Ethnic group and gender were not significantly

different between groups. Inhaled corticosteroid use was also similar in both groups. There was no significant difference between groups in the number of patients who were not diagnosed with asthma prior to the visit (patients who were not on bronchodilators or inhaled corticosteroids at the time of the visit). There was no significant difference in baseline lung function (FVC%, FEV_1%, FEV_1/FVC, and $FEF_{25–75\%}$) between the two groups (Table 1). As shown in Figure 1A, there were also no differences in the changes following two or four puffs of albuterol in percentage predicted values for FVC (4.3±0.8% vs 4.0±0.7%, respectively), FEV_1 (10.0±1.1% vs 10.5±1.1%, respectively), or $FEF_{25–75\%}$ (30.2±2.9% vs 33.5±2.9%, respectively). Given the concern that bronchodilator responsiveness could have been blunted by patients with baseline normal spirometry, subset analysis of patients with a baseline FEV_1 of ≤80% predicted was conducted. In this potentially more responsive subgroup, there were also no differences in the changes in any spirometry parameter following two or four puffs of albuterol (Figure 1B).

Similarly, there was no significant difference in the assessment of a positive bronchodilator response between the two groups, with a positive bronchodilator response in 53% (n=61) of patients receiving two puffs of albuterol and a positive response in 62% (n=77) of patients receiving four puffs of albuterol (OR 1.42; 95% CI 0.85–2.37; *P*=0.19; Table 2). There was also no significant difference in bronchodilator response between the two-puff and four-puff groups in children with baseline FEV_1 values ≤80% predicted, with a positive bronchodilator response in 85% (n=22) of two-puff patients and a positive bronchodilator response in 75% (n=21) of four-puff patients. Additional subgroup analysis found no difference in bronchodilator responsiveness for two or four puffs of albuterol based on patient race or whether or not they were receiving inhaled

Table 1 Baseline characteristics of patients receiving two puffs of albuterol and four puffs of albuterol

Characteristic	Two puffs (n=115)	Four puffs (n=125)	*P*-value
Age (years)	8.6 (SD 3.0)	8.7 (SD 2.1)	0.57
Gender (%F:%M)	43:57	38:62	0.43
Ethnic group (%C:%AA:%H)	51:16:30	53:15:30	0.83
ICS (% on)	77	66	0.08
Baseline %FVC	101% (IQR 92–109%)	99% (IQR 91–107%)	0.31
Baseline $\%FEV_1$	91% (IQR 82–100%)	90% (IQR 81–98%)	0.42
Baseline FEV_1/%FVC	84% (IQR 79–89%)	83% (IQR 78–87%)	0.067
Baseline $\%FEF_{25–75}$	77% (IQR 61–99%)	77% (IQR 58–91%)	0.23

Note: Data are presented as mean and standard error values for normally distributed parameters and as median and IQRs for non-normal parameters.
Abbreviations: AA, African American; C, Caucasian; F, female; $FEF_{25-75\%}$, forced expiratory flow; FEV1; forced expiratory volume in one second; FVC, forced vital capacity; H, Hispanic; ICS, inhaled corticosteroid; M, male.

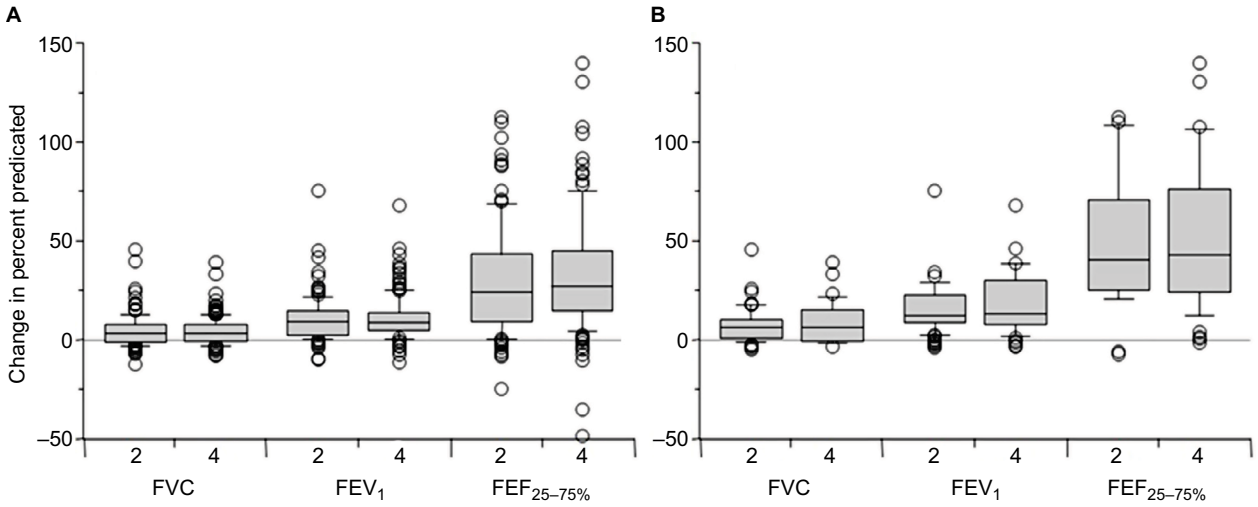

Figure 1 Box plots of absolute change in percentage predicted spirometry values in patients receiving two vs four puffs of albuterol.
Notes: (**A**) All patients. (**B**) Patients with baseline FEV_1 values ≤80% predicted.
Abbreviations: $FEF_{25-75\%}$, forced expiratory flow; FEV1; forced expiratory volume in one second; FVC, forced vital capacity.

corticosteroids at the time of spirometry testing (Table 2). Of interest, however, when we divided patients by age, we found that patients aged ≤8 years (the median age for the entire group) were 2.4 times more likely to respond to four puffs than two puffs of albuterol (OR 90% CI 1.3–4.52), while patients aged >8 years were not (OR 90% CI 0.48–1.70). This age affect could not be attributed to differences in FEV_1 responses (11.5±1.4% vs 9.2±1.4% increases with four vs two puffs of albuterol in patients aged ≤8 years [*P*=0.26], compared to 9.7±1.5% vs 11.2±1.5% in patients aged >8 years [*P*=0.51]) but was due to an enhanced $FEF_{25–75\%}$ response in the younger children (40.4±4.7% vs 27.3±3.8% increases with four vs two puffs of albuterol in patients aged ≤8 years [*P*=0.030], compared to 27.8±3.6% vs 34.7±4.3% in patients aged >8 years [*P*=0.22]).

In light of the similar results for two puffs and four puffs of albuterol, we went on to conduct noninferiority analysis for two puffs vs four puffs relative to our predetermined change in FEV_1 of 6% predicted. This range is defined by the shaded region in Figure 2. As can be seen, the one-sided CI for the difference in FEV_1 responses between two and four puffs of albuterol lay within the 6% lower limit of acceptability for the entire group of patients – demonstrating noninferiority two puffs vs four puffs of albuterol in changing FEV_1 values. Noninferiority was also demonstrated for each of subgroup comparison, except for children with baseline FEV_1 values ≤80% predicted. While the FEV_1 response to two puffs of albuterol was not significantly less than that to four puffs of albuterol in this subgroup (ie, Figure 1B), there were insufficient numbers of patients with low baseline FEV_1 values to establish noninferiority of the two-puff response.

Discussion

In this retrospective study, we found similar changes in FEV_1 (% predicted) and in overall bronchodilator responsiveness in patients receiving two puffs of albuterol and patients receiving four puffs of albuterol. Additional subgroup analysis showed no difference in FEV_1 changes or in bronchodilator responsiveness in children with baseline FEV_1 values ≤80%, children receiving or not receiving inhaled corticosteroids, or children of Caucasian or non-Caucasian ancestry. Interestingly, subgroup analysis of subjects aged ≤8 years revealed that more subjects in the four-puff group had a significant bronchodilator response than those in the two-puff group. In the absence of differences in FEV_1 changes between the two albuterol doses in this age group, the difference in bronchodilator response assessment was attributed to greater changes in $FEF_{25–75\%}$ values in young children following four puffs than two puffs of albuterol. This finding may indicate that four puffs of albuterol should be considered for the determination of bronchodilator response in young children.

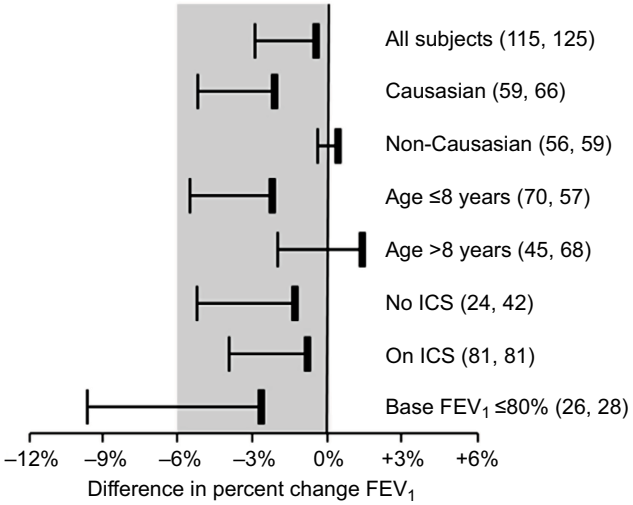

Figure 2 Comparison of FEV_1 responses to two puffs of albuterol and four puffs of albuterol in all subjects and subgroups of subjects.
Notes: Data depict mean values (heavy bars) and 95% one-sided CIs for the difference in responses. Gray zone demonstrates noninferiority margin. Numbers in parentheses give number of subjects in each group receiving two and four puffs of albuterol, respectively.
Abbreviations: FEV_1; forced expiratory volume in one second; ICS, inhaled corticosteroid.

Table 2 Comparison of positive bronchodilator responses in subjects receiving two or four puffs of albuterol

Condition	Two-puff response (n)	Four-puff response (n)	OR (*P*-value)	OR 90% CI
All subjects	53.0% (115)	61.6% (125)	1.42 (0.19)	0.92–2.19
FEV_1 ≤80%	84.6% (26)	75.0% (28)	0.55 (0.50)	0.17–1.72
Caucasian	40.7% (59)	54.6% (66)	1.75 (0.15)	0.96–3.18
Non-Caucasian	66.1% (56)	69.5% (59)	1.17 (0.84)	0.61–2.26
Age ≤8 years	51.4% (70)	71.9% (57)	2.42 (0.028)	1.30–4.52
Age >8 years	55.5% (45)	52.9% (68)	0.90 (0.85)	0.48–1.70
No ICS	50.0% (24)	66.7% (42)	2.00 (0.20)	0.85–4.73
On ICS	50.6% (81)	59.3% (81)	1.42 (0.34)	0.84–2.39

Note: OR depicts chance of responding to four vs two puffs albuterol.
Abbreviations: FEV_1; forced expiratory volume in one second; ICS, inhaled corticosteroid.

The current ATS guidelines recommend the use of four puffs of albuterol to ensure "that the response is high on the albuterol dose–response curve".[3] However, this recommended dose was based on expert opinion rather than empiric data and the guidelines are not specific to the pediatric population. In fact, the ATS guidelines for lung function test interpretation indicate that in the determination of bronchodilator response, there is no consensus about the drug, dose, or mode of administering a bronchodilator in the pulmonary function laboratory.[5] The current Global Initiative for Asthma guidelines suggest that a bronchodilator response should be determined following 200–400 μg of salbutamol.[6] Additionally, 160 μg of ipratropium bromide can be used to determine bronchodilator response and "other drugs can also be used".[3] Despite stating that "standardizing the bronchodilator dose administered is necessary in order to standardize the definition of a significant bronchodilator response", the ATS guidelines do not provide a preferred bronchodilator.[3]

The lack of bronchodilator dose standardization for pediatric patients is reflected in many large, well-known pediatric asthma studies including the Childhood Asthma Management Plan study that all used two puffs of albuterol for the determination of bronchodilator response in pediatric patients.[7–9] Another major study used two puffs of albuterol (180 μg) or one vial of 0.083% nebulized albuterol (2,500 μg) to determine bronchodilator responsiveness.[10] It is estimated that 2,500 μg of albuterol via nebulizer provides an albuterol dose that is equivalent to 4–10 puffs of albuterol via metered dose inhaler (MDI) with spacer.[11,12] It is possible that the ATS guidelines suggest a range of albuterol dosing rather than a standard dose because it is unclear what dose of bronchodilator is needed to ensure the accuracy of bronchodilator response.

Similarly, the ATS guidelines do not provide age-specific recommendations for bronchodilator dose to be used in the assessment of bronchodilator response. The ATS guidelines provide estimates of amount of bronchodilator dose delivered in adult patients with use of a metered-dose inhaler with spacer.[3] It is noted that "for children, pulmonary deposition is less than that in adults", but there are no estimates provided regarding deposition of bronchodilator in pediatric patients.[3,14] If decreases in pulmonary deposition are less than the decrease in size of smaller patients, it is possible that young children could receive disproportionately higher pulmonary doses of albuterol than older children and adults. If so, the higher relative doses of albuterol could account for the greater bronchodilator responsiveness seen following four puffs of albuterol in our younger children. Perhaps, then, even higher doses of albuterol (eg, six to eight puffs) should be used in older children and adults to ensure maximum bronchodilator effectiveness.

Clearly, use of higher doses of albuterol would be associated with a greater incidence and severity of side effects. The ATS guidelines state that a lower dose of albuterol can be used if there are concerns about side effects such as tachycardia and tremors.[3] If two puffs of albuterol are equivalent to four puffs of albuterol in the determination of a bronchodilator response, then two puffs of albuterol could be used for the assessment of reversible airway obstruction and the two puffs of albuterol would likely result in decreased dose-related side effects. Administration of two puffs would also result in less time and cost expenditures than the administration of four puffs of albuterol in a busy clinic setting.

In addition to diagnostic purposes, bronchodilator responsiveness has important clinical implications that may impact a patient's treatment plan. Sharma et al[7] found that a consistent bronchodilator response over time was associated with poorer clinical outcomes including higher number of emergency room visits, higher number of hospital admissions, and more frequent need for prednisone bursts. This information may lead to a more aggressive asthma treatment plan for a patient with a positive bronchodilator response due to concern for a potential increased risk for a severe asthma exacerbation. While bronchodilator responsiveness may affect treatment choices,[15] it is important to note that our study compared two puffs vs four puffs of albuterol for the determination of bronchodilator response; it did not evaluate the use of two vs four puffs of albuterol for asthma treatment purposes.

There are a few limitations to this study. The retrospective nature of the study relied on information documented in the patient's chart at the time of the initial visit. We were unable to determine if minor side effects from albuterol were experienced by patients, as reactions such as tachycardia and tremor were not routinely documented in clinical visits and vital signs were not taken pre- and postalbuterol administration. Also, this was an observational study and causation cannot necessarily be implied from association. Additionally, the population in this study was predominately Caucasian and predominately male, which may make it difficult to apply these findings to pediatric patients with asthma in general. While all patients were coached in MDI and spacer technique by a respiratory therapist in the pulmonary function laboratory, we were also unable to determine how differences in patient performance of the technique could have affected responses. For example, if younger children were less effective users of MDI and spac-

ers, diminished delivery of albuterol could have resulted in a subtherapeutic pulmonary dose following inhalation of two puffs of albuterol and thereby enhanced the relative response seen with four puffs. While it was not possible to control for longitudinal trends during the study period, the respiratory therapist staff was stable during the time period of this study. It is not possible to determine which patients in the two-puff group received albuterol with a chlorofluorocarbon (CFC) inhaler and which patients in the two-puff group received albuterol with a hydrofluoroalkane (HFA) inhaler. The propellant used in the inhaler CFC or HFA could theoretically alter the deposition of the albuterol in the airways. CFC inhalers were no longer sold in the USA after December 31, 2008, so all patients in the four-puff group received albuterol HFA. There are additional factors known to affect bronchodilator responsiveness such as allergy status, vitamin D status, and β-adrenergic haplotypes that could not be evaluated due to the retrospective nature of this study.

Currently, there is no consensus regarding drug, dose, or delivery method of bronchodilator in the determination of bronchodilator response in pediatric patients with asthma. Based on mean change in FEV_1 and overall assessment of bronchodilator responsiveness, administration of two puffs of albuterol for postbronchodilator spirometry testing in our population of pediatric asthmatic patients was not inferior to the administration of four puffs of albuterol. This finding suggests that a patient who has a bronchodilator response will have a response regardless of the dose of albuterol. Therefore, it may be possible to use lower doses of albuterol to identify positive bronchodilator response and potentially decrease the dose-dependent side effects of albuterol and the time spent administering albuterol in the clinic setting. Additional studies with larger populations that are more reflective of general asthma population are needed to determine if two puffs of albuterol are adequate to determine bronchodilator response.

Acknowledgment

Preliminary results of this study were presented as a poster at the 2013 American Thoracic Society Conference in Philadelphia, Pennsylvania, PA, USA, on May 20, 2013.

Disclosure

The authors report no conflicts of interest in this work.

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