Repeat Dosing of Albuterol via Metered-Dose Inhaler in Infants With Acute Obstructive Airway Disease

A Randomized Controlled Safety Trial

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Background: Airway obstruction and bronchial hyperactivity oftentimes lead to emergency department visits in infants. Inhaled short-acting β_2-agonist bronchodilators have traditionally been dispensed to young children via nebulizers in the emergency department. Delivery of bronchodilators via metered-dose inhalers (MDIs) in conjunction with holding chambers (spacers) has been shown to be effective.

Study Objective: Safety and efficacy evaluations of albuterol sulfate hydrofluoroalkane (HFA) inhalation aerosol in children younger than 2 years with acute wheezing caused by obstructive airway disease.

Methods: A randomized, double-blind, parallel group, multicenter study of albuterol HFA 180 μg (n = 43) or 360 μg (n = 44) via an MDI with a valved holding chamber and face mask in an urgent-care setting. Assessments included adverse events, signs of adrenergic stimulation, electrocardiograms, and blood glucose and potassium levels. Efficacy parameters included additional albuterol use and Modified Tal Asthma Symptoms Score ([MTASS] reduction in MTASS representing improvement).

Results: Overall, adverse events occurred in 4 (9%) and 3 (7%) subjects in the 180-μg and 360-μg groups, respectively. Drug-related tachycardia (360 μg) and ventricular extrasystoles (180 μg) were reported in 1 patient each. Three additional instances of single ventricular ectopy were identified from Holter monitoring. No hypokalemia or drug-related QT or QTc prolongation was seen; glucose values and adrenergic stimulation did not significantly differ between treatment groups. In the 180-μg and 360-μg groups, mean change from baseline in MTASS during the treatment period was −2.8 (−49.8%) and −2.9 (−48.4%), and rescue albuterol use occurred in 4 (9%) and 3 (7%) subjects, respectively.

Conclusions: Cumulative dosing with albuterol HFA 180 μg or 360 μg via MDI-spacer and face mask in children younger than 2 years did not result in any significant safety issues and improved MTASS by at least 48%.

Key Words: albuterol, hydrofluoroalkane, spacer, face mask

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BACKGROUND

In 2004, children with asthma in the United States accounted for 750,000 visits to the emergency department (ED) and a total of 198,000 hospitalizations.[1] Asthma prevalence among children in the United States remains at historically high levels, with the disease affecting 8.9% of children aged 0 to 17 years (6.5 million), of which 1.4 million are aged 0 to 4 years.[2] Data show that almost half of all children hospitalized for asthma or wheezing are younger than 6 years, and nonatopic wheezing associated with an acute viral infection is likely the most common cause.[2,3] Among all the available therapies, the first strategy is the use of reliever medications such as β_2-agonists (albuterol) that reverse acute airway obstruction, providing rapid relief in the management of these acute episodes.[4–6]

Inhaled short-acting β_2-agonist bronchodilators have traditionally been dispensed via nebulizers in the ED. Recently, delivery of bronchodilators via metered-dose inhalers (MDIs) in conjunction with holding chambers (spacers) has been shown to be more advantageous than nebulizers in terms of efficiency, lower costs, portability, and ease of use[7–11] while producing equivalent or superior bronchodilation to nebulized treatment even in cases of severe airway obstruction.[9,12,13] In children older than 2 years, bronchodilator therapy with an MDI-spacer combination resulted in a shorter length of stay in the ED, lower heart rates, and less severe adverse effects than the use of nebulizers.[12,14] Safety data regarding repeat bronchodilator multiple-dose therapy in children younger than 2 years are limited, and the use of MDIs with spacers has not been well evaluated in this age group in an acute care setting. Although efficacy measures were included, the primary objective of this study was to assess the safety of albuterol sulfate hydrofluoroalkane (HFA) inhalation aerosol in children younger than 2 years with acute wheezing caused by obstructive airway disease.

METHODS

Participants

In this randomized, double-blind, parallel-group, multicenter controlled trial, the safety and efficacy of 2 albuterol doses (180 or 360 μg) were evaluated in children with a history of symptomatic wheezing who presented with an acute wheezing episode caused by suspected obstructive airway disease. Ethics committee approval and written informed consent were obtained before study start. Sixteen EDs and clinics in the United States

participated in this study, enrolling approximately 5 subjects per site (ranging from 1 to 16). The location of these clinics covered 12 states that geographically represented different regions throughout the United States. Clinic personnel received training in study procedures including protocol-required assessments and Holter monitoring at a central investigator meeting.

Male and female subjects younger than 2 years, who presented with symptoms of acute wheezing consistent with obstructive airway disease, were considered for the study. An informed consent was signed by the subject's legally acceptable representative before study participation. Enrollment was monitored to ensure that 30 subjects completed at least 3 treatment dosing periods in each treatment arm and that a minimum of 15 subjects were younger than 1 year. To be eligible for the study, subjects had to be younger than 24 months at randomization with a history of at least 1 prior episode of symptomatic wheezing. Subjects were required to have a baseline symptom score between 4 and 9 based on the Modified Tal Asthma Symptoms Score ([MTASS] calculated by adding the scores for each of the 4 variables: respiratory rate, wheezing, cyanosis, and accessory respiratory muscle utilization as shown in Table 1)[15] and a pulse oximetry measurement greater than 88% while breathing room air.

Children were excluded from the study if they had experienced a life-threatening asthma/wheezing episode, respiratory symptoms requiring admission to the intensive care unit within the past 3 months, 2 or more ED visits or hospital admissions within the past 3 months, a history of intubation for respiratory distress, known pulmonary or cardiac congenital malformations or a history of or current significant disease, fever (rectal temperature ≥100.5°F or 38°C) at screening, significant laboratory test abnormalities at screening, born before 34 weeks of gestation, drug allergies to any β-agonist, sympathomimetic drug or component of any MDI formulation, or received an investigational drug in the past 30 days.

Study Design

The randomization was generated using random numbers generated by Web server–based clinical trial randomization system. Each treatment number was allocated to one of the 2 (albuterol sulfate 180 or 360 μg) treatment groups using appropriate blocking within each stratum (ie, ratio of 1:3 for age range, birth to younger than 12 months or 12 months to younger than 24 months). The treatment codes and treatment allocations were supplied to Covance's (Princeton, NJ) Interactive Voice Response Service for interactive allocation of treatment. In the event of an emergency or a serious adverse event that required knowledge of the subject's treatment regimen, the investigator could follow appropriate procedures to unblind the subject.

All eligible children were randomized and received treatments of either albuterol sulfate HFA (Ventolin HFA, GlaxoSmithKline, Research Triangle Park, NC) inhalation aerosol 180 μg (2 inhalations of albuterol sulfate HFA 90 μg [Can A] + 2 inhalations of HFA propellant placebo [Can B]) or 360 μg (2 inhalations of albuterol sulfate HFA 90 μg [Can A] + 2 inhalations of albuterol sulfate HFA 90 μg [Can B]) administered via a valved holding chamber (AeroChamber Plus, Monaghan Medical, Plattsburgh, NY) with attached face mask in the clinic. The study medication was administered as 2 inhalations from each can (Can A and Can B) at 20-minute intervals in the first hour, with the next 2 subsequent treatments given at 60-minute intervals for a total of 6 doses. After each puff, subjects were allowed approximately 8 breaths from the holding chamber. If acute respiratory symptoms improved (MTASS ≤2, O_2 saturation ≥95%, and no signs and symptoms of respiratory distress) after any scheduled dose, the child was excluded from further scheduled treatment. Systemic or inhaled corticosteroids and supplemental oxygen were permitted during the study. Other drugs such as inhaled anticholinergics, subcutaneous terbutaline, and/or subcutaneous epinephrine could be administered in the second and third hour if deemed necessary by the investigator. If a child required additional (rescue) albuterol (albuterol HFA inhalation aerosol 180 μg equivalent to 2 puffs) during treatment, the next scheduled study drug treatment was administered at least 15 minutes after rescue albuterol use. Need for rescue albuterol use was determined by the investigator. Requirement of more than 2 rescue albuterol treatments during the 3-hour treatment period was documented and resulted in the child being withdrawn from the study. A follow-up phone call was conducted approximately 5 to 7 days after treatment to assess the subject's health status.

Measures

Study assessments included demographic data, medical and asthma history, safety and efficacy measurements conducted at baseline (assessment 1) and every 20 minutes for the first hour, every 30 minutes for the next 2 hours, and at end of study treatment for a total of 10 assessments.

Safety measures included continuous 6-lead electrocardiogram (Holter) monitoring, 10 second electrocardiogram (ECG) measurements (at baseline and each dosing assessment), assessment of adverse events (including severity and duration), pulse oximetry, vital signs (including pulse rate, diastolic and systolic blood pressure, temperature, and respiratory rate), physical examination by a licensed health care professional (to preclude variability in measurements, the same individual tried to perform both the screening and end of study examinations), clinical laboratory tests for blood glucose and serum potassium, and signs

TABLE 1. Modified Tal Asthma Symptom Score[15]

Score	Respiratory Rate (breaths/min)		Wheezing*	Cyanosis	Accessory Muscle Use
	<6 mo	>6 mo			
0	≤40	≤30	None*	None	None
1	41–55	31–45	Terminal expiration with stethoscope only	Circumoral with crying only	+
2	56–70	46–60	Entire expiration and inspiration with stethoscope only	Circumoral at rest	++
3	>70	>60	Expiration and inspiration without stethoscope	Generalized cyanosis at rest	+++

*If wheeze not audible because of minimal air entry, consider score 3.

+ indicates low; ++, medium; +++, high.

and symptoms of adrenergic stimulation (evaluated as pulse rate from vital signs showing an increase of ≥20% from baseline, sinus tachycardia recorded as adverse event, and investigator's judgment). Adverse events were considered "related" or "not related" to study drug per the investigator's judgment.

Vital signs and adrenergic stimulation assessments were conducted prestudy and poststudy medication administration at all assessments except assessments 1 (baseline), 6, 8, and 10 (end of treatment) (ie, nondosing assessment times). Blood samples for serum potassium and glucose were obtained before randomization and at the end of the treatment period and drawn from the patient by a heel prick and analyzed using an I-Stat handheld blood analysis system.

The primary efficacy end point was the mean percent change from baseline during the entire treatment period in the MTASS. The MTASS (Table 1) and pulse oximetry assessments were conducted at baseline, every 20 minutes for the first hour after administration of the first dose, every 30 minutes for the next 2 hours, and at end of study treatment or premature discontinuation. Other efficacy parameters included the change from baseline in MTASS during the entire treatment period and additional (rescue) albuterol use over and above study medication.

Statistical Analysis

The primary population was the intent-to-treat population (all randomized subjects who received at least 1 dose of study medication). Analysis of all safety and efficacy data was based on this population.

Because the primary objective of this study was to evaluate the safety of albuterol sulfate HFA inhalation aerosol, a sample size of 60 completed subjects (30 per treatment group) was judged adequate to provide sufficient safety information for this population. Inferential statistics (*P* values or confidence intervals) were used for descriptive purposes only and should not be interpreted for inferential significance. All statistical tests were 2-sided, with treatment differences at or less than the 0.05 level of significance being considered nominally significant without regard to any issues of multiplicity. Statistical analyses were performed using SAS Version 8.0 in a UNIX environment (SAS Institute Inc, Cary, NC). Analysis of adverse events was performed using Fisher exact test, whereas analyses of ECG parameters and MTASS were performed using analysis of covariance adjusting for baseline value, investigative site, age, and sex. In addition, paired *t* tests were performed for the percent change from baseline in MTASS within each treatment group.

RESULTS

Characteristics of Study Subjects

A total of 110 subjects presented with an episode of acute bronchospasm out of which 87 subjects were randomized to double-blind treatment (Fig. 1). Slightly more subjects (Table 2) in the 180-μg group (29 [67%]) discontinued from the study compared with the 360-μg group (23 [52%]) primarily because they were discharged because of good response (27 [63%] and 20 [45%] in the 180- and 360-μg groups, respectively). Other reasons for premature discontinuation during the treatment period were protocol violations and consent withdrawn. The most common protocol violation category was "other," which included laboratory not done or not repeated, patient discontinued before meeting good responder criteria, follow-up done later than scheduled, and blood pressure or MTASS not assessed. Two (5%) and 3 (7%) subjects in the 180-μg and 360-μg groups, respectively, had treatment medication violations (missed doses or dose given at incorrect times).

Baseline demographic characteristics (Table 3) were similar across the treatment groups with the exception of gender. Thirty (70%) of 43 subjects were male in the 180-μg group compared with 27 (61%) of 44 subjects in the 360-μg group. Mean weight was similar across treatment groups (range, 9.2–9.6 kg).

Safety

The incidence of noncardiac adverse events was low in both treatment groups (Table 4). Serious adverse events of wheezing (1 patient) and bronchial hyperactivity and respiratory syncytial virus infection (1 patient), both in the 360-μg group, were not

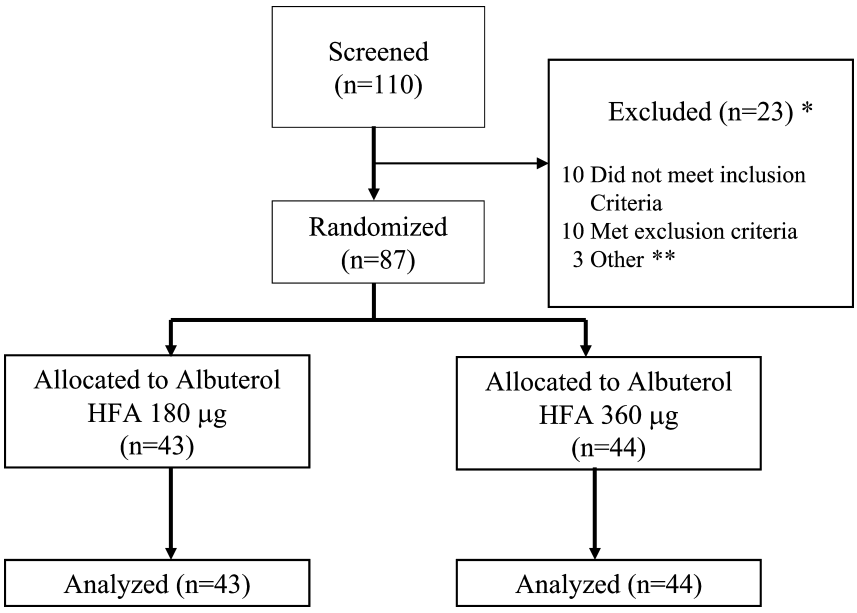

FIGURE 1. Patient enrollment data. *Subjects may have more than 1 reason for exclusion. **Other, rectal temperature greater than 100.5°F or tympanic temperature greater than 101.5°F, born before 34 weeks of gestation.

TABLE 2. Patient Disposition

	Albuterol HFA 180 μg, n = 43	Albuterol HFA 360 μg, n = 44
Completion status, n (%)		
Completed	14 (33)	21 (48)
Discontinued	29 (67)	23 (52)
Reason for P/D, n (%)		
Good response	27 (63)	20 (45)
Adverse event	0	0
Consent withdrawn	0	1 (2)
Lack of efficacy	0	0
Protocol violation	2 (5)	2 (5)

P/D indicates premature discontinuation.

considered study drug related by the investigator, and both subjects completed the study. No significant changes from baseline were seen in blood pressure, body temperature, or pulse oximetry in either treatment group. At end of study treatment, the mean respiratory rate decreased by approximately 10 breaths/min in both treatment groups.

No significant abnormalities were observed during continuous Holter monitoring. Seven subjects in the 180-μg group and 2 subjects in the 360-μg group had Holter abnormalities that were not considered to be significant. These included a single ventricular ectopy, which occurred in 3 subjects in the 180-μg and 1 patient in the 360-μg treatment groups, and a supraventricular ectopy, which occurred in 6 subjects in the 180-μg group and no subject in the 360-μg group. Two subjects in the 180-μg group reported both these conditions. Compared with baseline, overall mean cardiac rates as determined by continuous Holter decreased by 0.9 in the 180-μg group and increased by 4.1 in the 360-μg group. At the end of study treatment, the heart rate determined by 10 second ECGs decreased by 1.8 beats per minute in the 180-μg group and increased by 3.3 beats per minute in the 360-μg group.

In addition to continuous Holter monitoring, 7 subjects in each treatment group had abnormal significant 10 second ECGs at the end of study treatment. In the 180-μg group, 6 of the 7 subjects had tachycardia, with 5 of these subjects having this abnormality at baseline. The seventh patient had sinus rhythm and premature systoles with ventricular indeterminate axis at the end of study treatment and sinus rhythm present at baseline. In the 360-μg group, 6 of the 7 subjects had tachycardia, and the remaining patient had sinus rhythm and an abnormal change (increase) of 78 milliseconds in QT, with a QT value of 334 milliseconds before study discontinuation (for good response). This event was not considered to be drug related by the investigator. Drug-related adverse events of tachycardia (360 μg) and ventricular extrasystoles (180 μg) were reported in 1 patient each. There were no significant changes from baseline at the end of study treatment in mean heart rate or mean QTc interval measures via ECG for either of the treatment groups (Table 5). No individual had a QT interval longer than 334 milliseconds, and no patient had a QTc interval longer than 427 milliseconds.

The overall incidence of adverse events possibly related to adrenergic stimulation was very low and occurred in a single patient each in the 180-μg (ventricular extrasystole) and 360-μg (tachycardia) groups. These events resolved on the same day and did not lead to patient withdrawal from the study. Five subjects in the 180-μg and 9 subjects in the 360-μg group had at least 1 postbaseline pulse rate of 20% or greater over baseline. One patient each in both treatment groups had this increase predose, whereas 2 subjects in the 180-μg group and 4 subjects in the 360-μg group were either agitated or crying during the

TABLE 3. Patient Demographics and Baseline Characteristics

Patient Characteristics	Albuterol HFA 180 μg, n = 43	Albuterol HFA 360 μg, n = 44
Mean age, mo (SD)	10.9 (6.29)	10.5 (6.33)
Median (range)	11.0 (1–23)	7.5 (2–21)
Birth to <12 mo, n (%)	24 (56)	25 (57)
12 mo to ≤24 mo, n (%)	19 (44)	19 (43)
Gender, male, n (%)	30 (70)	27 (61)
Ethnicity/race		
White/black/other, n	19/10/14	20/11/13
History of maternal asthma, n (%)	11 (26)	10 (23)
MTASS, mean (SE)	5.7 (0.19)	5.8 (0.19)
Pulse rate/min, mean (SD)	142.1 (20.99)	142.0 (24.30)

The MTASS (range, 0–12) was calculated by adding the scores of each of the 4 variables: respiratory rate, wheezing, cyanosis, and accessory muscle utilization.

TABLE 4. Noncardiac Adverse Events During Treatment

Adverse Event	Albuterol HFA 180 μg, n = 43	Albuterol HFA 360 μg, n = 44	*P**
Patients with any AE, n (%)	4 (9)	3 (7)	0.713
Patients with any noncardiac AE, n (%)	3 (7)	2 (5)	0.676
Bronchial hyperactivity	0	1 (2)	
Nasal congestion	1 (2)	0	
Rhinorrhea	1 (2)	0	
Pyrexia	1 (2)	1 (2)	
Respiratory syncytial virus infection	0	1 (2)	

*P values are based on Fisher exact test.

AE indicates adverse event.

TABLE 5. Heart Rate and QTc Prolongation

Measure	Albuterol HFA 180 μg, n = 43	Albuterol HFA 360 μg, n = 44
Heart rate, beats per min		
Baseline mean (SE)	152 (3.15)	149.7 (3.23)
End of treatment* mean (SE) 95% CI (−7.3 to 11.8)	152.4 (3.80)	154.7 (4.09)
QTc†, ms		
Baseline mean(SE)	350.8 (4.03)	350.6 (3.17)
End of treatment* mean (SE) 95% CI (−18.6 to 9.0)	350.8 (5.52)	346.0 (5.95)

Treatment comparisons based on analysis of covariance adjusting for baseline value, investigative site, age, and gender.

*End of study treatment or premature discontinuation.

†QTc was measured using the Fredericia (QTint/cubed root of RR interval) formula.

procedure. Increased pulse rates in the remaining subjects were not considered clinically relevant by the investigator.

Serum potassium and blood glucose levels at baseline and end of study treatment in both treatment groups were evaluated. An increase in glucose values was reported in 13 subjects, with a mean increase of 13.6 mg/dL in the 180-μg group and 21.1 mg/dL in the 360-μg group. Mean serum potassium values decrease by 0.3 mEq/L and 0.5 mEq/L in the 180-μg and 360-μg groups, respectively. These differences were not considered clinically significant by the investigators.

Efficacy

The mean percent change in the MTASS score from baseline during the entire treatment period demonstrated significant improvements ($P < 0.001$) for each of the 2 treatment groups; however, there was no difference ($P = 0.739$) in improvement between the 2 treatment groups. The 180-μg treatment group showed a mean percent change of −49.8% (least squares mean change from baseline, −2.8); and for the 360-μg group, a mean percent change of −48.4% (least squares mean change from baseline, −2.9). Few subjects required additional nonstudy rescue albuterol use, 4 (9%) and 3 (7%) subjects in the 180-μg and 360-μg groups, respectively. The mean dose for rescue albuterol during treatment was 288 μg and 1340 μg in the 180-μg and 360-μg groups, respectively. A single subject was admitted to the hospital for observation and continuation of treatment.

DISCUSSION

Results of this study demonstrate that repeat cumulative doses of 180 μg or 360 μg albuterol HFA administered via an MDI with valved holding chamber and an attached face mask to children younger than 2 years was well tolerated. There were no clinically significant adverse effects such as hypokalemia, increased heart rate, adrenergic stimulation, or QT prolongation. The MTASS improved by at least 48%, with 9% of subjects or less in either treatment group requiring rescue albuterol in addition to study medication. During the study, the total mean study medication excluding rescue medication use was 770 μg and 1636 μg for the albuterol 180-μg and 360-μg groups, respectively, and these were well tolerated.

These results are consistent with other studies demonstrating that the use of MDI with spacer and face mask is an effective alternative for the administration of bronchodilators to young children in an emergency setting.[9,10,16–19] A recent meta-analysis of 6 clinical trials in children younger than 5 years treated with β_2-agonists for wheezing or asthma revealed that the use of MDIs with auxiliary devices was more effective than nebulizers in significantly improving clinical scores (nearly 40%) and decreasing hospitalization rates, especially in children with more severe asthma or wheezing.[20] A recent review of spacers versus nebulizers for β_2-agonist treatment in 1076 children aged 2 years and older demonstrated that spacer use was associated with a significantly shorter length of stay in the ED as compared with that for nebulizers.[12] Several comparative studies in children younger than 2 years have shown that the administration of bronchodilators with an MDI-spacer in an emergency care setting provides greater or equivalent improvement in lung function compared with nebulizers.[14,21,22]

In the current study, the primary efficacy measures of percent change from baseline in the MTASS improved (≥48%) in both treatment groups. This measure has been found to be useful in evaluating the severity of acute wheezing episodes in infants. However, some studies have reported conflicting results with regard to the correlation of the individual elements of the composite scores with other clinical features of acute asthma such as ausculatory findings or hypoxemia.[23–25] Pulse oximetry has been shown to correlate closely with the MTASS clinical score in children younger than 24 months of age.[15] Most subjects needed an average of 4 doses or an hour of treatment to attain a good response to therapy that required no further treatment. This was consistent with the study by Leversha et al,[10] where a median of 4 treatments was required. Similarly, in the study reported by Rubilar et al,[21] subjects with similar ages and treatment responded faster (within 1 hour of treatment) in the MDI-spacer group. Another indicator of treatment efficacy in the current study was the low incidence of rescue albuterol use (<9%) in both treatment groups. Moreover, most of the subjects (27 and 20 subjects in the albuterol 180-μg and 360-μg groups, respectively) were discharged because of good response and did not require further treatment. Three and 2 subjects in the albuterol 180-μg and 360-μg groups, respectively, continued treatment for respiratory distress, and a single subject in the albuterol 360-μg group was admitted to the hospital.

In terms of systemic adverse effects after β_2-agonist treatment, several studies in young children have reported greater increases in heart rate with the use of nebulizers than with MDI-spacers.[9,10,14,17,26] Unresolved asthma and increased systemic absorption caused by greater facial and oropharyngeal deposition of medication by nebulizers versus improved targeting of medication to the lungs by spacers have been postulated to be contributory factors.[10] Kerem et al[16] attributed a decrease in heart rate in their study to the clinical advantage of using an MDI with spacer over a nebulizer. In the current study, overall, there were no clinically significant changes in heart rate or QTc measures.

The β_2-receptor–mediated electrolyte disturbances include hypokalemia from cellular influx of potassium into cells or hyperglycemia caused by increased glycogenolysis.[27–29] High doses of β_2 agonists can cause a rapid decrement in serum potassium levels,[30,31] although factors such as concomitant use of steroids or theophylline[32] or hypoxemia[33] can also contribute to hypokalemia. Despite concomitant use of steroids, subjects in our study did not experience hypokalemia. In our study, baseline pulse oximetry was measured, and no significant changes were observed in pulse oximetry. Increases in blood glucose levels observed in some subjects were not attributed to study medication.

There were several limitations to this study. The administration of bronchodilator therapy in infants is often difficult in an urgent care setting because of patient acuity and complications occurring during therapeutic interventions. Parents presenting as legal guardians expressed concern over certain invasive repeat measurements such as blood draws and ECG and Holter monitoring. The latter procedures were also difficult to conduct in subjects with small body frames or those under distress, which may have increased the variability in the measurements. The MTASS was evaluated based on clinical impression of the individual parameters, which may be a cause of variation for this measure. Interpretation of the efficacy data could be limited because subjects were not required to demonstrate reversibility at entry. Because this study was primarily a safety study, statistical tests of efficacy end points were performed for informational purposes only. The subjects studied were of a defined age and severity; therefore, the results may not be generalizable to other populations. The small number of subjects studied prevents ruling out very rare events that could be associated with albuterol use in this population. Despite these limitations, this study provides useful safety and efficacy data to consider in the context of managing infants with acute respiratory symptoms requiring urgent care.

Our data suggest that administration of repeat doses of albuterol HFA aerosol via an MDI-spacer combination with face mask seems to be a well-tolerated treatment modality for respiratory symptoms consistent with acute bronchospasm in children younger than 2 years in an ED setting.

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