

Efficacy and safety of inhaled bitolterol mesylate via metered-dose inhaler in children with asthma

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Background: There have been numerous studies in asthmatic adults demonstrating the efficacy and safety of bitolterol mesylate metered-dose inhaler; however, only one additional study has examined bitolterol metered-dose inhaler in pediatric asthma.

Objective: To establish the safety and effectiveness of bitolterol mesylate metered-dose inhaler at one, two, and three inhalations in pediatric asthmatic patients 4 to 12 years of age.

Methods: A multicenter, double-blind, randomized, crossover, placebo-controlled, dose-ranging study. Forty-six patients were evaluated in three centers. Patients were stratified by age, 4 to 6, 7 to 9, 10 to 12 years at each center. One, two, or three inhalations were administered along with an additional double-blind, randomized, placebo dose. Bronchodilation was defined as a 15% or greater increase in FEV₁ over baseline. Onset, maximum improvement, and duration of action were obtained for each patient. Serial pulse rate, blood pressure, and respiratory rate determinations were obtained for each patient.

Results: Onset within five minutes occurred in 56.6% to 71% of patients, depending on the dose. Mean maximum improvement, which was dose dependent, overall ranged from 28.2% to 40.3% with a peak response in 66.7 to 69.8 minutes. A direct relationship of magnitude with regard to dose of bitolterol was observed, ($P < .001$). A significant correlation, $r = .732$, in response between bronchodilation and baseline FEV₁ was observed ($P < .001$). Median duration of action ranged from three to four hours in responding patients across all doses. Up to 31% of patients had durations greater than eight hours after three inhalations. Adverse effects were reported in five of 46 patients for all doses with mild transient tremor occurring in two patients, 4.3%. Also, there was little effect on pulse rate, 2.2%.

Conclusion: Bitolterol is an effective bronchodilator with durations of activity up to eight hours and minimal adverse effects in children.

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INTRODUCTION

Bitolterol, a specific beta₂-agonist, is administered as a “pro-drug” which is hydrolyzed to the active moiety, colterol, by esterases in the tissue and blood (Fig 1).^{1–5} The long duration of action and beta₂ selectivity of bitolterol may be attributed to the structural

uniqueness of the molecule, whereby a large N-alkyl substituent and di-p-toluate esters decrease susceptibility to inactivation by monoamine oxidase and catechol-o-methyltransferase, respectively. The N-alkyl substituent also contributes to the beta₂ selectivity of bitolterol. These chemical properties, along with the high esterase activity in pulmonary tissue as opposed to cardiac tissue, result in a high concentration of the active drug in the lung and a prolonged bronchodilator activity with negligible side effects.^{1–5}

Bitolterol mesylate has been shown in clinical trials to produce safe and effective long-acting bronchodilation in asthmatic adults when administered by a metered-dose inhaler. Numerous single

and multiple dose studies in adults have demonstrated that most patients had a rapid onset of action within five minutes and a duration of action ranging from four to more than eight hours.^{1–5}

Asthma is the leading chronic disease of childhood in industrialized countries.⁶ Despite advances in treatment, both mortality and morbidity rates from childhood asthma are increasing.⁶ In children under 17 years of age, asthma is the leading cause of school absenteeism from chronic disease.⁷ Interference with school in turn has a major impact on asthmatic children in terms of academic achievement; therefore, an obvious objective of pharmacologic therapy would be to keep school absenteeism to a minimum.

Beta₂-agonists are extremely useful in the management of acute asthma, in the prophylaxis of exercise induced bronchospasm, and for maintenance therapy of chronic asthma in children.⁸ Although oral beta₂-agonists are effective in the long-term management of childhood asthma, the advantages of administering these drugs by the inhaled route include a more rapid onset of action, lower dosage requirements, and a lower incidence of systemic side effects.⁸

This is the first study conducted with bitolterol metered-dose inhaler in pediatric patients in the 4- to 12-year age bracket. It has been observed in clinical practice that much of the beta-agonist utilization via metered-dose inhaler is in the pediatric population.⁹ The objective of this study was to determine whether children exhibit a bronchodilator response with bitolterol metered-dose inhaler similar to that seen in adults at the usual adult dose without undue side effects.

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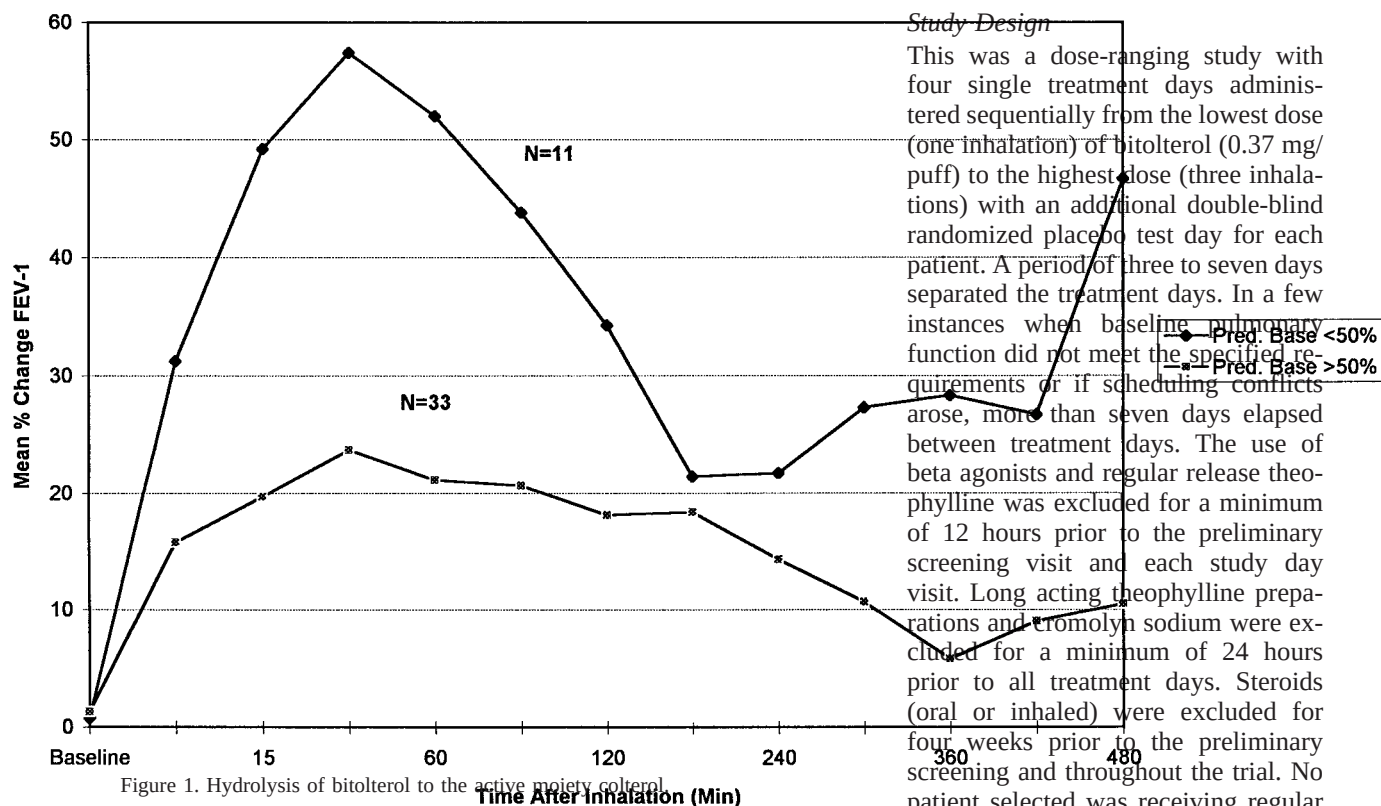
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MATERIALS AND METHODS

Patient Selection

This study was a multicenter, double-blind, randomized, crossover, placebo-controlled dose-ranging study conducted in asthmatic patients ranging from 4 to 12 years. A total of 46 patients were evaluated. Patients were stratified by age group into three groups, 4 to 6 years, 7 to 9 years, and 10 to 12 years. Fifteen patients were studied at each of three centers (five patients per age group) with the exception of one site where a sixth patient was added to the oldest age group.

All patients selected had a diagnosis of bronchial asthma confirmed by history, physical examination, and pulmonary function tests prior to the start of the study. As part of the screening criteria each patient had to demonstrate baseline stability and reversibility of airway obstruction. To determine stability, the pretreatment FEV₁ values (−30, −15 minutes) were to be within 20% of the time zero FEV₁. Revers-

ibility was demonstrated by a 20% increase in FEV₁ at either the 5-, 10-, or 20-minute time interval following two inhalations from a standard isoproterenol metered-dose inhaler delivering a total dose of 0.262 mg. The patients underwent a physical examination, standard 12-lead EKG plus a 1-minute rhythm strip. Vital sign determinations and laboratory analysis (hematology, biochemistry, and urinalysis) were conducted within 1 week before the start of the study treatments. A chest radiograph was obtained, if it was necessary, to differentiate or to confirm the presence of related conditions. None of the patients had a diagnosis of renal or hepatic disease, cardiac failure, polycythemia, angina or arrhythmias, hyperthyroidism, diabetes mellitus, or a convulsive disorder. No patients smoked during or previous to the study.

The Institutional Review Board at each study center approved the study, and written consent was obtained from the parents of each participating patient.

Bitolterol mesylate aerosol was provided in metered-dose inhalers. Each canister contained a volume of 15 mL and each actuation released 0.37 mg of bitolterol mesylate. Each inhaler (canister and mouthpiece) was identical in appearance and was provided in a plain, white carton. The placebo aerosol was provided in an identical metered-dose inhaler containing a volume of 15 mL. The formulation of the placebo was identical except for the absence of bitolterol mesylate. Packaging and labeling were also identical.

The patients received two canisters for each treatment day, canister A and canister B, to allow double-blinding of the placebo treatment. Each canister was labeled with the patient code number, treatment number, and a designation of either A or B. The patients inhaled one actuation from canister A, and two actuations from canister B on each test day. A placebo treatment was randomized among one of the four test days by a computer generated code. On the other three treatment days, the

Table 1. Demographic Characteristics

Center	Age Group, yr	F	M	Age, yr*	Duration of Asthma, yr*	Screening FEV ₁ , L*	Screening FEV ₁ % Pred*
A	4-6	1	4	5.7 ± 0.4	3.2	0.84 ± 0.12	63.76 ± 12.25
	7-9	0	5	8.0 ± 0.9	5.4	1.05 ± 0.39	56.14 ± 16.23
	10-12	1	5	11.6 ± 0.3	9.0	1.59 ± 0.44	63.75 ± 9.81
B	4-6	2	3	5.2 ± 0.7	2.8	0.69 ± 0.18	59.12 ± 17.19
	7-9	1	4	8.0 ± 0.6	3.4	1.06 ± 0.39	53.82 ± 11.18
	10-12	1	4	11.4 ± 0.8	4.6	1.78 ± 0.17	73.18 ± 6.37
C	4-6	2	3	5.8 ± 0.4	4.4	0.75 ± 0.22	58.65 ± 14.81
	7-9	1	4	8.8 ± 0.4	5.8	1.11 ± 0.35	53.84 ± 13.98
	10-12	3	2	11.0 ± 0.9	6.4	1.57 ± 0.48	64.14 ± 17.48
Overall	4-6	5	10	5.5 ± 0.6	3.5	0.76 ± 0.18	58.85 ± 15.39
	7-9	2	13	8.2 ± 0.7	4.9	1.07 ± 0.36	54.61 ± 13.98
	10-12	5	11	11.1 ± 0.7	6.8	1.64 ± 0.38	66.85 ± 12.49
All Patients		12	34	8.4 ± 2.4	5.0	1.17 ± 0.51	60.23 ± 14.96

* Mean ± Standard Deviation.

Table 2. Mean Baseline FEV₁ and Mean Percent of Predicted Normal FEV₁ by Dose* Overall

	Placebo	Inhalations of Bitolterol		
		1	2	3
No. patients	46	46	44	44
Mean baseline FEV ₁ , L	1.22 ± 0.5	1.2 ± 0.5	1.17 ± 0.5	1.16 ± 0.4
Mean baseline % predicted normal	62.8 ± 16.9	61.7 ± 17.3	60.9 ± 16.3	61 ± 14.7

* Expressed as mean ± standard deviation.

patients received single treatments with sequentially increasing doses of bitolterol mesylate (one, two, and three inhalations).

On each treatment day the aerosol canisters were actuated by the investigator or a designated staff member at least once prior to administration to assure that the units were functioning properly. Each patient had previously demonstrated proficiency in the use of metered-dose aerosol. The patients actuated their own inhalation canisters on all study days.

Assessment of Efficacy

Efficacy was assessed with serial spirometric pulmonary function tests before and after the administration of test medication. On each of the four treatment days the FEV₁ (forced expiratory volume in one second), FEF_{25-75%} (forced mid-expiratory flow), FVC (forced vital capacity), and PEFR (peak expiratory flow rate) were recorded at each observation time (1, 5, 15, 30, 60, 90, 120, 180, 240, 300, 360, 420, and 480 minutes).

Emphasis was given to FEV₁ as the critical parameter of bronchodilator activity with respect to onset, maximum improvement, and duration of action. Onset of bronchodilator activity was defined as the first time an increase in FEV₁ of at least 15% over the baseline (time 0) within the first 90 minutes occurred. Maximum improvement was defined as the maximum FEV₁ response in the first four hours over the baseline. If a patient had no improvement over baseline, then zero was used for this patient's maximum improvement. Duration of action was defined as the total length of time during which FEV₁ was increased greater than 15% over baseline. If a patient had no onset within 90 minutes after the administration of the medication, then zero was used for the patient's duration. Once two FEV₁ values were less than or equal to 15% over baseline, then no further time was added to the duration, even if later FEV₁ observations were above 15% over baseline.

The variables onset, maximum improvement, duration, and average improvement were obtained for each patient from their response curve which was determined by linear interpolation between the FEV₁ responses at the observation times 0, 5, 15, 30, 60, 90, 120, 180, 240, 300, 360, 420, and 480 minutes. Forced vital capacity, FEF_{25-75%}, and PEFR were also analyzed in the same manner as FEV₁.

Assessment for Safety

Serial pulse rate, blood pressure, and respiratory rate determinations were taken at the same observation times the efficacy determinations were made up to and including eight hours postmedication. These readings were obtained on each treatment day. On each treatment day, the electrocardiogram and 1-minute rhythm strip were also obtained 30 minutes before and 30, 60, and 120 minutes after medication. After each treatment, the investigator evaluated any changes in pulse rate, blood pressure, electrocardiograms, and adverse events to determine

Table 3. Mean Maximum Percent Increase From Baseline*

Age Groups, yr	Inhalations of Bitolterol		
	1	2	3
4–6	30.5 ± 25.6	33.4 ± 20.66	36.8 ± 18.25
(15)†	(15)	(15)	(15)
7–9	32.6 ± 21.56	42.6 ± 26.91	49.2 ± 26.55
(15)	(15)	(15)	(15)
10–12	21.8 ± 13.1	27.7 ± 19.68	34.5 ± 21.52
(16)	(16)	(14)	(14)
Overall	28.2 ± 22.03	34.7 ± 23.63	40.3 ± 22.76
(46)	(46)	(44)	(44)

* Expressed as mean ± standard deviation.

† (n) = number of patients.

whether the medication was tolerated and whether further treatments could be administered. Complete hematology, urinalysis, and blood chemistries were also performed at the conclusion of the trial. All adverse events were recorded on each study day.

Statistical Analysis

A dose-response curve was generated for each patient by linear interpolation between all the FEV₁ post-treatment measurements. Mean and median onset, magnitude, and duration of action are obtained from these measurements. Onset of action is defined as the increase in FEV₁ that is greater than 15% above baseline within the first 90 minutes. Magnitude of bronchodilation was defined as the maximum increase in FEV₁ in the first four hours of treatment. Duration of action is based on the total length of time for which FEV₁ was greater than 15% above baseline up until two consecutive values were

less than or equal to 15% above baseline. The median duration of bronchodilation was estimated by the Kaplan-Meier analysis. Duration of action is analyzed in responding patients as well nonresponders. Also, a linear regression analysis was performed to examine the correlation between baseline FEV₁ and maximum response after three inhalations.

Since the placebo treatment was randomized among the four test days, an analysis was carried out to determine whether the FEV₁ response was influenced by study day. The placebo response in terms of maximum and average improvement as a percent of baseline on each study day was analyzed with the Kruskal-Wallis test for equality of distribution of improvement.

RESULTS

A total of 46 patients (34 males and 12 females) enrolled in the study. Their

demographic characteristics are listed in Table 1. Two patients withdrew from the study. One patient withdrew after the two treatment days when parents felt he could not miss additional school days. Another patient withdrew on the third treatment day prior to treatment due to a fainting spell unrelated to study procedures. Consequently, the efficacy and safety analysis took 46 patients into consideration for placebo and the one inhalation regimen, while 44 patients were included for the two and three inhalation regimens. Also, there was a greater than 7-day period between the pre-study examinations and the first test day involving six patients due to scheduling conflicts and delays in availability of study supplies. The data from the demographic characteristics at the three centers were similar for each of the three age groups.

The mean baseline FEV₁ across the age groups before the start of the

Table 4. Median Duration of Action (hrs)

Age Group, yr	Inhalations of Bitolterol		
	1	2	3
Responding Patients			
4–6	2.9 (10)	1.8 (13)	1.2 (14)
7–9	1.8 (11)	4.3 (12)	5.8 (12)
10–12	3.9 (9)	3.8 (9)	4.1 (12)
Overall Responders	3.1 (30)	3.6 (34)	2.9 (38)
All Patients			
4–6	0.4 (15)	1.5 (15)	1.2 (15)
7–9	1.8 (15)	4.0 (15)	3.7 (15)
10–12	0.5 (16)	1.6 (14)	2.6 (14)
Overall All Patients	0.8 (46)	1.8 (44)	2.4 (44)

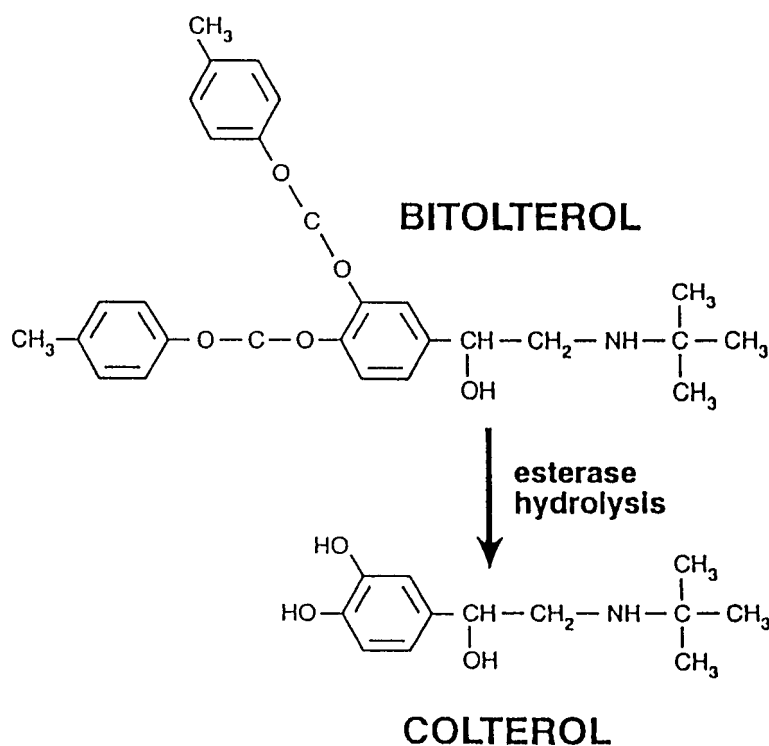


Figure 2. Mean percent increase in FEV₁ over baseline at each test time after inhalation of bitolterol.

study ranged from 54.6% to 66.8% of predicted normal. The overall mean baseline for each dose is listed in Table 2. The overall degree of pre-treatment airway obstruction involving all age groups remained relatively constant on the four test days ranging from 1.16 to 1.22 L. Also, the overall mean percents of predicted normal FEV₁ varied little on the four study days with a range of 60.9% to 62.8%. Differences in baseline airway obstruction were observed when considering specific age groups. For example, the mean percent of predicted normal FEV₁ for the oldest group across all study days (65.4% to 68.1%) was higher than the 4 to 6 year olds (59.4% to 60%) and the 7 to 9 year old group (57.5% to 60.3%). These differences were not of statistical significance and these differences did not effect appropriate interpretation of the results. Regarding the analysis for study day effect, the Kruskal-Wallis test for

equality of the distribution of the maximum and mean improvement as a percent of baseline over the four test days yielded *P* values of .84 and .76, respectively. In essence, there was no evidence that placebo maximum and mean improvement was influenced by the study day.

Efficacy

Onset of action, maximum improvement, and duration of activity are presented in this study. All doses resulted in rapid onset of bronchodilator activity. Onset of action within five minutes occurred in 56.6% to 71% of patients and within 90 minutes in 65.2% to 86.5% of patients, depending on the dose. The median times to onset for one, two, and three inhalations of bitolterol were 4.0, 3.7, and 3.3 minutes, respectively.

The mean maximum improvement overall ranged from 28.2% ± 22.03 at one inhalation to 40.3% ± 22.76 at three inhalations compared with 15.2%

± 14.6 for placebo. The overall summary in Table 3 shows a direct relationship of increasing magnitude with regard to increasing dose of bitolterol. The mean maximum percent improvements for the four doses are significantly different (*P* < .001). There is a linear increase in maximum percent improvement to increasing dose (*P* < .001). There is no evidence of difference between the age groups in their improvements to increasing doses (*P* = .395) or their general level of response (*P* = .259). The overall time to mean maximum improvement in FEV₁ over baseline was consistent with the three treatments, 69.8 ± 63.5, 66.7 ± 52.5, and 69.7 ± 56.3 minutes for one, two, and three inhalations, respectively. The overall mean maximum improvements in FEV₁ are noted in Table 3. In summary, there is a significant linear dose response with no differences in response between age groups.

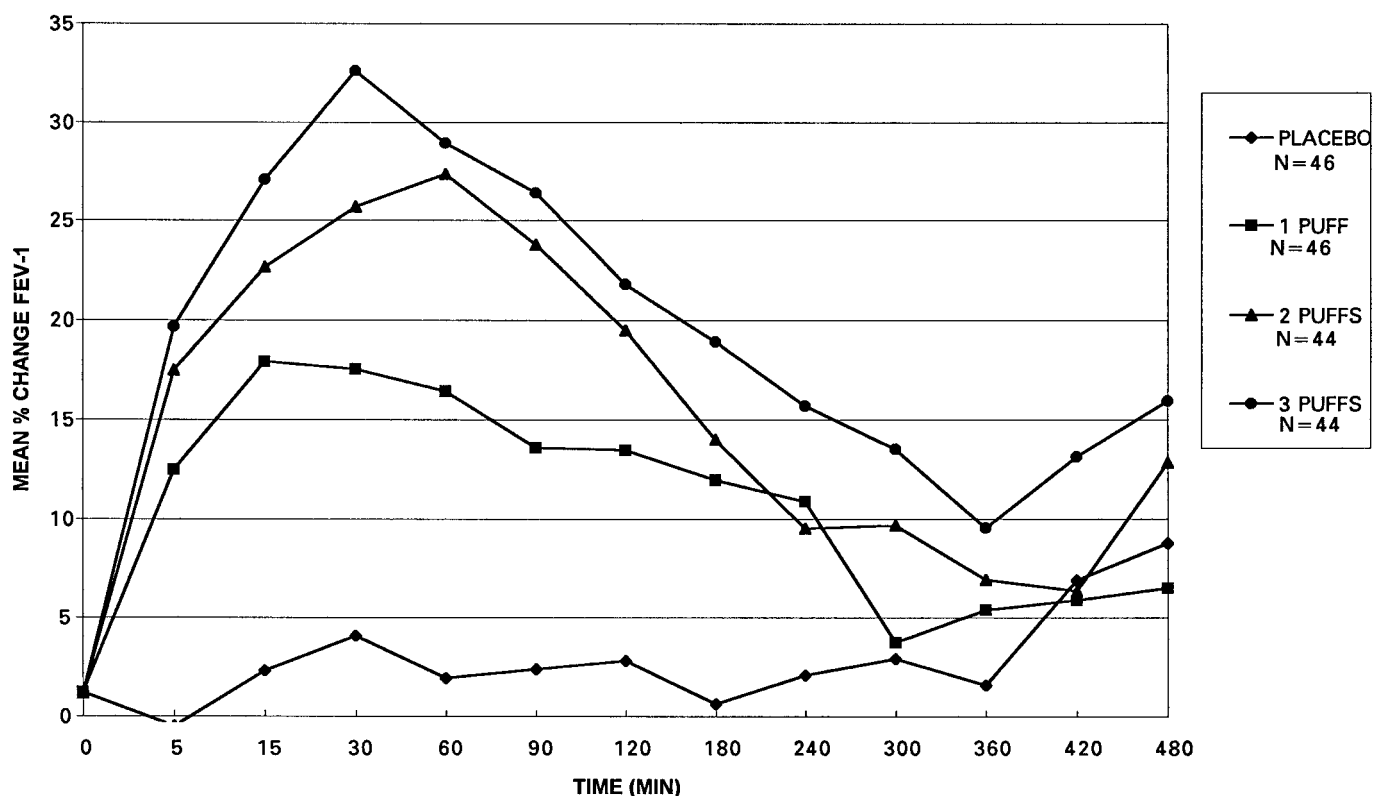


Figure 3. Regression line of the maximum percent increase in FEV₁ as compared with baseline FEV₁ (percent predicted normal) after three inhalations of bitolterol.

The overall Kaplan-Meier estimated median duration of clinically significant bronchodilation (defined by an increase in FEV₁ of 15%) is presented in Table 4. The median duration of action ranged from three to four hours in responding patients, but the median duration of action for these patients did not increase in a dose dependent manner: 3.1, 3.6, and 2.9 hours for one, two, and three inhalations of bitolterol, respectively. The median duration of action, however, inclusive of all patients, did increase in a dose related manner. The mean percent changes in FEV₁ observations are presented in Figure 2. Also, 31% of patients had a duration greater than eight hours after three inhalations. There was a significant correlation in the response depending on baseline FEV₁ with lower baselines being associated with a greater response (Fig 3). Figure 4 il

lustrates the differential in bronchodilation between patients with a low baseline, FEV₁ <50% of predicted normal, as compared with patients with a higher baseline, FEV₁ >50% of predicted normal, after three inhalations of bitolterol. The mean duration of action for patients with mean FEV₁ values less than 50% of predicted normal was eight hours or more after the three inhalations as compared with the three to four hour mean duration for patients with baselines equal to or greater than 50% of predicted normal.

In addition to the FEV₁ values obtained at each observation time, FVC (forced vital capacity), FEF_{25-75%} (forced mid-expiratory flow rate), and PEFR (peak expiratory flow rate) were also obtained. The results of these analyses were similar to those obtained in the analysis of FEV₁.

Safety

The incidence of adverse effects that occurred with each treatment is presented in Table 5. The incidence of adverse effects was low with all doses. Mild tremor was noted in two patients. The tremor was transient and lasted one to two hours. One patient experienced mild sinus tachycardia with placebo treatment. This represented the only adverse event with placebo. Mild throat irritation was noted in one patient after receiving three actuations of bitolterol. One patient experienced emesis four hours after receiving one inhalation of bitolterol. The event was mild in severity and the relationship to the medication is unknown.

Other reported adverse events that were not related to bitolterol were headache, sinusitis, rhinitis, and syncope.

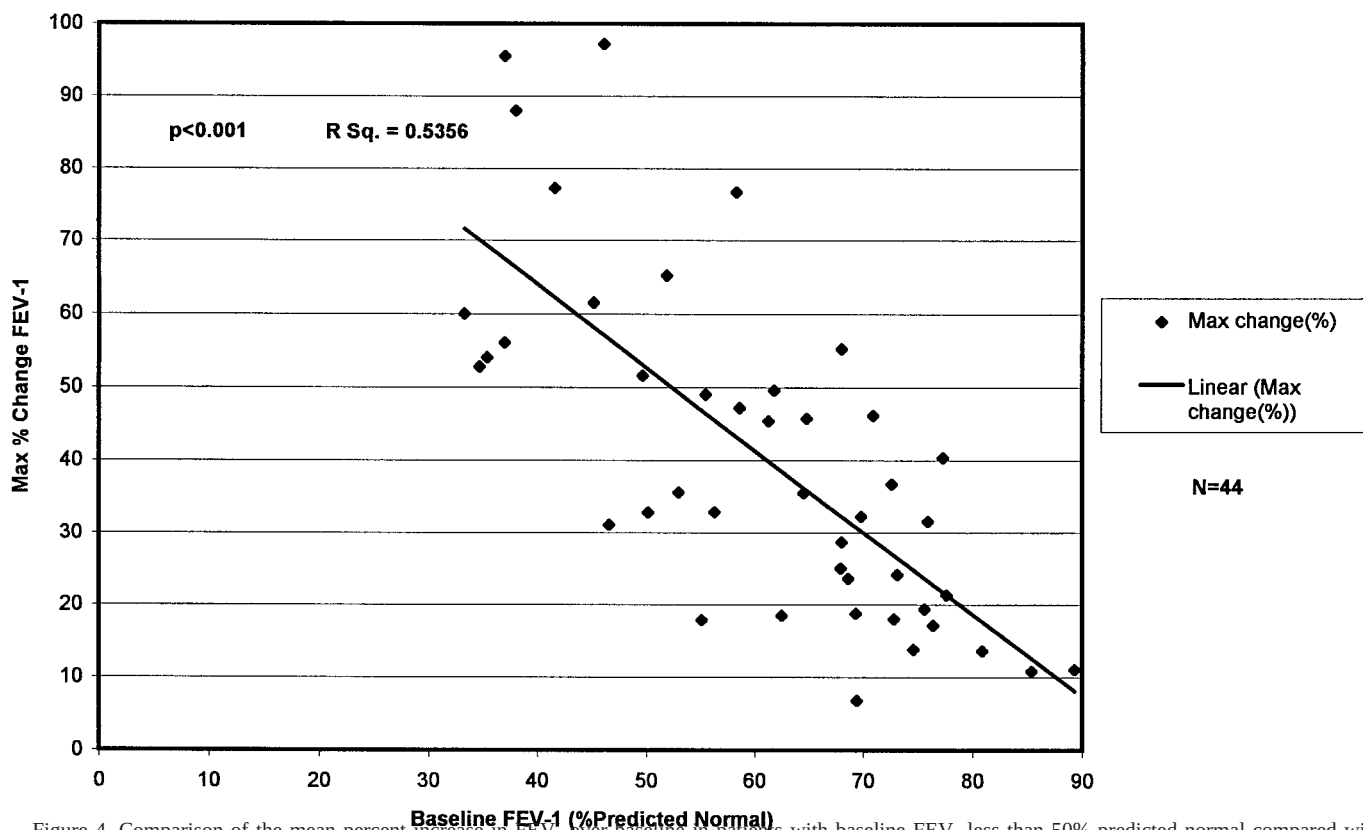


Figure 4. Comparison of the mean percent increase in FEV₁ over baseline in patients with baseline FEV₁ less than 50% predicted normal compared with patients with baseline FEV₁ greater than 50% predicted normal after three inhalations of bitolterol.

Table 5. Overall Incidence of Adverse Events

Adverse Event	Placebo n = 46	Inhalations of Bitolterol		
		1 n = 46	2 n = 44	3 n = 44
Tachycardia	1	0	0	0
Tremor	0	1	0	1
Throat irritation	0	0	0	1
Vomiting	0	1	0	0

n = total number of patients.

Mean maximum increases in pulse rate are presented by dose in Table 6. Treatments with one, two, or three inhalations of bitolterol had little effect on pulse rate. Mean maximum pulse rate increases ranged from 8.4 to 13.1 beats per minute across all treatment doses. There was little difference in mean systolic blood pressure between the placebo treatment and the three inhalations of bitolterol. Overall mean percent increases ranged from 6.4 to 8

mm Hg across all dosage groups. Mean diastolic blood pressure indicates little or no differences between the placebo treatment and one, two, and three inhalations across centers and within age groups. The overall range of mean maximum increases in diastolic pressure was 6.9 to 8.2 mm Hg across all doses.

There were no significant changes in electrocardiograms or clinical laboratory parameters.

DISCUSSION

Aerosol therapy with beta₂-agonists has become a recognized mode of treatment of bronchial asthma in children.^{6-8,10,11} In general, the goal of treatment of asthma in children is to provide sufficient symptom control that will permit normal school attendance, full participation in recreational activities, uninterrupted sleep at night, minimal use of hospital facilities, and reasonably normal pulmonary func-

Table 6. Mean Maximum Increase in Pulse Rate from Baseline (beats/min)

Age Groups, yr	Placebo	Inhalations of Bitolterol		
		1	2	3
4-6	10.1 (15)	9.1 (15)	11.7 (15)	7.0 (15)
7-9	11.1 (15)	7.3 (15)	14.7 (15)	11.3 (15)
10-12	7.8 (16)	8.8 (16)	13.0 (14)	10.6 (14)
Overall	9.6 (46)	8.4 (46)	13.1 (44)	9.6 (44)

(n) = Number of patients.

tion.¹⁰ Although there have been a number of studies evaluating the use of beta-agonist aerosols in children,^{12-16,20-22} the majority of studies have been conducted in adults. This study involves the use of bitolterol mesylate delivered by metered-dose inhaler in children ages 4 to 12 years.

This dose-ranging study is one of two studies performed with bitolterol mesylate metered-dose inhaler in children. A study evaluating the efficacy of long-term repetitive dosing with two inhalations of bitolterol three times daily in children has been published.¹⁶ Also, a study demonstrating the efficacy and safety of bitolterol mesylate inhalation solution via continuous flow nebulization in pediatric asthmatic patients was recently published.¹⁷ This single dose ranging study is being presented to validate further and document the optimal safe and effective dose of bitolterol mesylate aerosol delivered by metered-dose inhaler in this group of young asthmatic patients.

In this study, 44 patients completed a double-blind, randomized, crossover, placebo-controlled study of bitolterol mesylate delivered by metered-dose inhaler. The range of inhalations of active medication was from one to three inhalations on separate days with a double-blind placebo dose-randomized among the active doses. The onset of bronchodilation was rapid with clinically significant bronchodilation occurring within five minutes with most patients. The mean maximum improvement ranged from 28.2% with one inhalation to 40.3% with three inhalations. By comparison, mean maximum increases in FEV₁ during a repetitive dosing, 6-week study in adults ranged from 22.3% to 29.3% in one

study³ to 35% to 40% in other studies.⁴⁻⁵ There was a significant increase ($P < .001$) in response between doses; however, there was no difference between age groups.

The median duration of action ranged from three to four hours in responding patients. This was similar to adult studies in which median duration of action was three to four and one-half hours.³⁻⁵ Although there was not a dose-dependent increase in responding patients, there was a dose-dependent increase when all patients were considered. Also, an estimated 31% of patients had durations of action greater than eight hours after three inhalations of bitolterol mesylate. Actually, all adult and pediatric investigations of bitolterol mesylate aerosol reported had a number of patients that experienced clinically significant bronchodilation for more than eight hours after treatment.

The incidence of adverse events was low with all doses with mild transient tremor occurring in two patients. The adverse events observed in this study were also comparable to those observed in the adult studies.^{2-5,19} Also, treatments with all doses of bitolterol had little effect on pulse rate with mean increases ranging from 8.4 to 13.1 beats per minute across all treatment doses.

While there was no statistical difference in response between age groups, the overall bronchodilator effect of bitolterol was greatest in the 7- to 9-year-old group and least in the 4- to 6-year-old group. The lower level of response in the younger age range may have been attributed to the high level of activity (play) demonstrated by the 4- to 6-year-olds and the lack of sustained

attention to performance of the FVC maneuvers over the 8-hour treatment day. Realistically, it is very difficult to encourage young children to cooperate with even a few spirometry maneuvers not to mention several days worth of testing. The greater effect observed in the 7- to 9-year-old group is probably attributable to the lower mean baseline FEV₁ in this group. Lower baseline values allow for a greater potential for improvement in pulmonary function compared with less obstructed patients.¹⁸ This is especially evident in Figure 3 which illustrates the correlation of low baseline FEV₁ levels with higher bronchodilator responses. This was observed across all age groups. Also, as observed in Figure 4, there was a greater response in both magnitude and duration in patients with baseline FEV₁ levels less than 50% predicted normal compared with patients with higher baseline levels. The impact of baseline on bronchodilator response was also evident in the long-term repetitive dosing pediatric study.¹⁶ In essence, impact of bronchodilation and duration of action in this study were effected by baseline pulmonary function status.

In conclusion, the results of this study indicate that one, two, and three inhalations of bitolterol mesylate aerosol (0.37 mg/actuation) are well tolerated and efficacious. The dose in pediatric patients may be the same as in adults, two inhalations with a third if necessary. Long-term studies would be needed to verify these findings.

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