

Comparison of Bitolterol Mesylate and Isoproterenol by Metered-Dose Inhaler for Regular, Long-Term Treatment in Asthmatic Children

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ABSTRACT

The objective of this study was to compare the efficacy and safety of bitolterol mesylate and isoproterenol hydrochloride, two sprays by metered-dose inhaler three times a day for 3 months in 240 asthmatic children ages 4–12 years. In this double-blind, randomized, parallel, multicenter study, patients received daily bitolterol mesylate or isoproterenol and were evaluated in the office at the beginning of the study and on 3 additional test days at 1-month intervals. They were evaluated by physical exam and ECG, blood and urine analyses, and spirometry for 8 hours after two sprays of the appropriate study aerosol. Theophylline was withheld for 24 hours and the study drug for 12 hours before office study days. All regular asthma medications were continued together with the bitolterol mesylate or isoproterenol between study days. Bronchodilation >15% above baseline occurred in <5 minutes with both treatments. Median durations of action were 3.1–4.4 and 1.2–2.2 hours with bitolterol mesylate and isoproterenol, respectively. Adverse effects were few and did not differ between drugs.

INTRODUCTION

BITOLTEROL MESYLATE is a specific β -agonist that has been shown to produce long-lasting bronchodilation in asthmatic adults when used as a metered-dose aerosol.⁽¹⁾ A single treatment with three sprays of bitolterol,⁽²⁾ and repetitive dosing for 6 weeks with three sprays

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tid,⁽³⁾ for 3 months with three sprays tid,⁽⁴⁾ and for 3 months with two sprays tid⁽⁵⁾ have demonstrated bronchodilation for 4 to more than 8 hours. A single treatment, dose-response study in children aged 4–12 years old who received one, two, or three sprays of bitolterol by metered-dose inhaler (MDI) revealed that the response was generally dose related, with the maximum effect after three inhalations. The mean duration of bronchodilation was 4 hours, although it persisted in some children for more than 8 hours.⁽⁶⁾ No long-term repetitive dose evaluation of β -agonist medication by MDI in children has been reported.

In this study, children in the 4 to 12-year age range were followed for three months using two sprays of bitolterol tid and their responses compared with those receiving two sprays tid of isoproterenol. Isoproterenol was chosen as the drug for comparison because it is the only β -agonist MDI which has been approved in the United States for use in children less than 12 years of age.

MATERIALS AND METHODS

Study design

This study was a multicenter, randomized, double-blind, parallel group study. A total of 242 children ages 4–12 years with moderate to moderately severe asthma requiring regular medications were evaluated in 10 centers for 3 months. Patients were stratified into two age groups, 4–8 years old and 9–12 years old. They were then randomized within each age group to receive either bitolterol two sprays tid (370 μ g/spray) or isoproterenol two sprays tid (85 μ g/spray) by MDI. Before starting the investigation, in addition to demonstrating reversibility, patients underwent a physical examination, vital sign determination, ECG, and laboratory analyses, including hematology, serum chemistries, and urinalysis. The qualifying patients were evaluated at the clinic at the start of the study (Test Day 1), and then at 1-month intervals for 3 months for a total of 4 test days. Throughout the study period, no β -agonist bronchodilators other than the bitolterol or isoproterenol inhalers were permitted; these were withheld for 12 hours before a test day. Patients for whom a theophylline preparation was prescribed continued to take it throughout the study; however, theophylline was withheld for 24 hours before a test day. Daily inhaled steroid aerosol or oral prednisone up to 10 mg every other day were permitted throughout the 3-month trial in those patients who were taking a constant dose of these medications.

Test days

On each test day spirometry was performed 30 and 15 minutes and immediately before use ($t = 0$) of two sprays of the study medications and at 5, 15, 30, 60, 90, and 120 minutes, then serially every 60 minutes for up to 8 hours. Vital signs were also obtained at these times. Patients underwent physical examination and ECG before medication and additional ECG at 30, 60, and 120 minutes after. In addition, 120 minutes after treatment, laboratory tests, including serum theophylline level assay, were performed. The aerosol medications were taken under the supervision of the investigator to confirm that the proper technique was used. Asthma severity, medication records, and adverse effects for the previous month of outpatient therapy were reviewed on each test day after Test Day 1. The FEV_1 was the main variable used to determine onset, maximum increase, and duration of bronchodilator activity. Onset of bronchodilator activity was defined as the time of increase of FEV_1 of >15% above baseline ($t = 0$). Duration of action was the total time during which FEV_1 was increased by 15% or more above baseline.

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RESULTS

Demographic characteristics of the patients, the duration of asthma, and concomitant medications were comparable among treatment centers and between treatment groups. Pooled data are presented in Table 1.

Mean baseline FEV₁ data as percent of predicted normal values⁽⁷⁾ were consistent with the diagnosis of moderate to moderately severe asthma; they are presented in Table 2. The mean baseline values were consistently higher in the younger children by comparison with the older children on each test day within treatment groups. The bitolterol-treated patients had higher mean baseline FEV₁ values on each test day than the isoproterenol-treated children in the same age group except for the 4 to 8-year-old children on Test Day 2. None of these differences was statistically significant.

The mean percent changes in FEV₁ for each treatment on the 4 test days for all children are depicted in Figs. 1-4.

TABLE 1. DEMOGRAPHIC DATA AND CONCOMITANT MEDICATION FOR THE TWO TREATMENT GROUPS

<i>Treatment</i>	<i>Bitolterol</i>	<i>Isoproterenol</i>
Number of patients		
Total	121	121
4-8 years	50	53
9-12 years	71	68
M/F	74/47	85/36
Mean age (years)	9.0	8.9
Mean duration of asthma (years)	6.1	5.9
Concomitant medication [number of patients (%)]		
Oral steroid	8(7)	4(3)
Aerosol steroid	16(13)	10(8)
Both steroids	2(2)	0
No steroids	95(78)	107(89)
Theophylline	90(74)	93(77)

TABLE 2. MEAN BASELINE FEV₁ (PERCENT OF PREDICTED NORMAL)

<i>Treatment</i>	<i>Test day</i>			
	<i>1</i>	<i>2</i>	<i>3</i>	<i>4</i>
Bitolterol				
4-8 years	68.9	65.0	68.8	70.7
<i>n</i>	50	48	47	46
9-12 years	62.6	64.7	64.9	65.9
<i>n</i>	71	69	66	64
overall	65.2	64.8	66.5	67.9
<i>n</i>	121	117	113	110
Isoproterenol				
4-8 years	61.9	67.0	66.3	66.5
<i>n</i>	52	51	46	46
9-12 years	59.9	60.3	61.8	61.7
<i>n</i>	67	61	56	54
overall	60.8	63.3	63.9	63.9
<i>n</i>	119	112	102	100

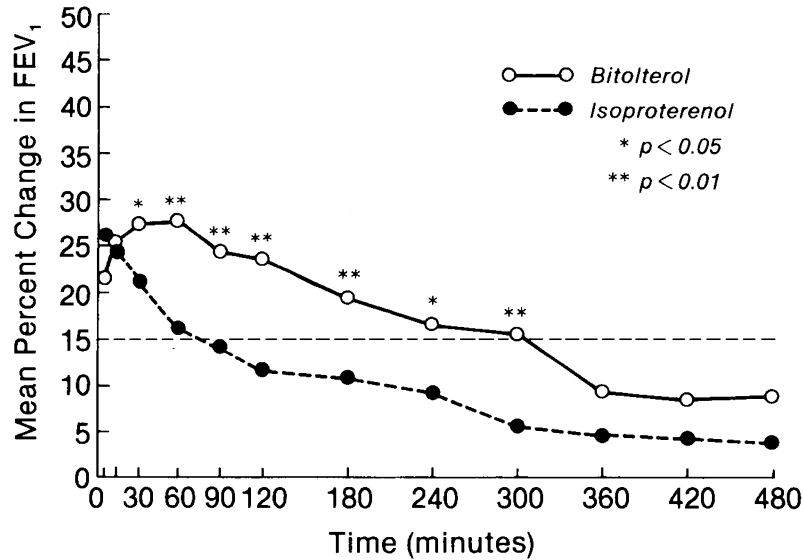


FIG. 1. Mean percent change in FEV₁ on Test Day 1.

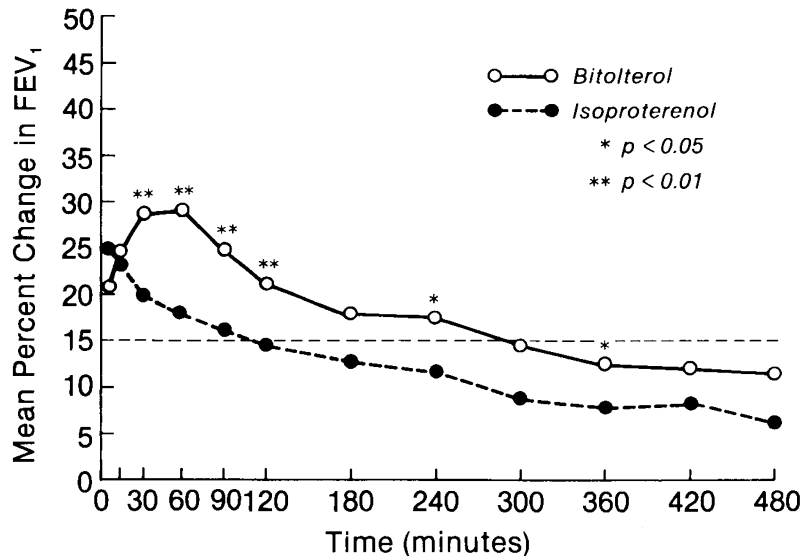


FIG. 2. Mean percent change in FEV₁ on Test Day 2.

Onset of bronchodilator activity was rapid with both treatments. Of the bitolterol-treated patients, 50–60% had a mean increase in FEV₁ >15% above baseline within 5 minutes by comparison with 61–72% of isoproterenol-treated patients. Absence of significant increase in FEV₁ above baseline was generally related to a higher baseline FEV₁.

The overall mean percent increases in FEV₁ for all patients combined following bitolterol treatments reached peaks of 25.3–29.2% above baseline at 30–60 minutes after therapy and remained ≥15% above baseline for 4–5 hours on the 4 test days. The mean peak increases following isoproterenol therapy were 25.1–27.3% above baseline, occurred at 5–15 minutes after treatment and decreased to ≤15% above baseline within 1–3 hours.

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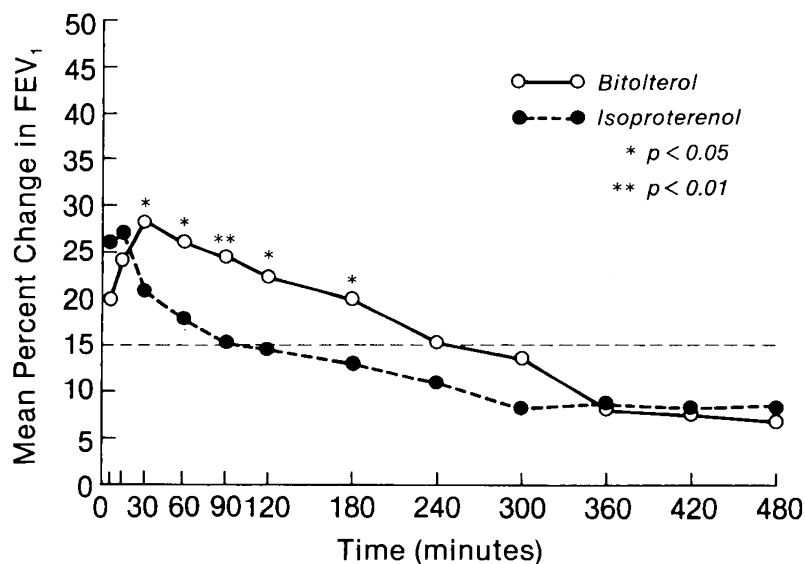


FIG. 3. Mean percent change in FEV₁ on Test Day 3.

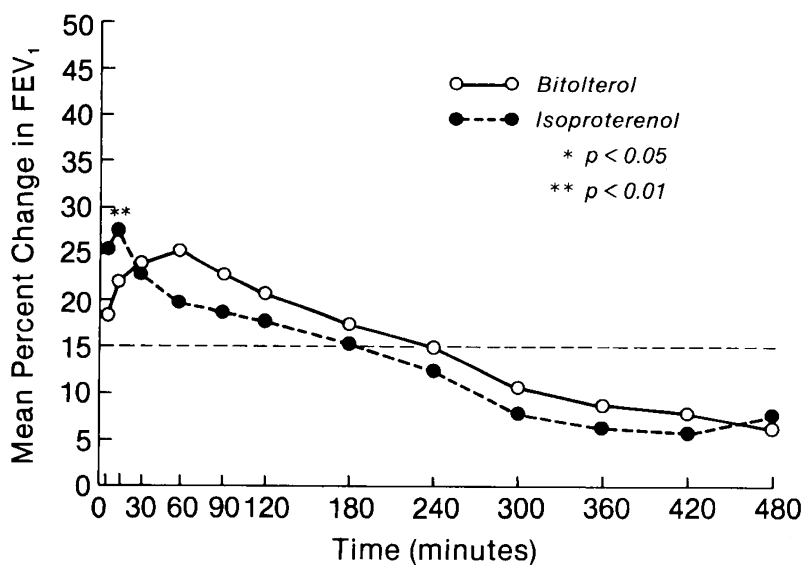


FIG. 4. Mean percent change in FEV₁ on Test Day 4.

The mean percent increases in FEV₁ in the 9 to 12-year-old children following bitolterol were consistently greater than those following isoproterenol on all 4 test days. Mean percent increases in the younger, 4 to 8-year-old children were greater following bitolterol than isoproterenol on Test Days 1, 2, and 3. On Test Day 4 in this younger group, the mean increases were similar following both bitolterol and isoproterenol treatments; however, the mean baseline FEV₁ was elevated in the bitolterol treated patients as shown in Table 2.

The individual patient mean maximum percent increases in FEV₁ were similar for the two medications over all four tests as shown in Table 3 with no statistically significant differences between treatments or test days. The median times of maximum improvement were 30, 60, 30,

TABLE 3. MEAN MAXIMUM PERCENT IMPROVEMENT IN FEV₁

Treatment	Test day			
	1	2	3	4
Bitolterol	34.0	34.7	34.0	31.3
Isoproterenol	33.5	32.1	32.4	33.5

and 60 minutes after bitolterol for Test Days 1–4, respectively, compared to 15 minutes after isoproterenol on all test days ($p < 0.05$).

The median durations of action, defined as the number of hours with $\geq 15\%$ increase in FEV₁ above baseline, were 4.4, 4.3, 3.7, and 3.1 hours following bitolterol for Test Days 1, 2, 3, and 4, respectively. The corresponding median durations of action following isoproterenol were 1.2, 1.7, 1.6, and 2.2 hours (Table 4). The greater median duration of action following bitolterol compared to isoproterenol was statistically significant on Test Days 1, 2, and 3 ($p < 0.05$) and was $p < 0.066$ on Test Day 4. There were no significant differences in the median duration of action between the younger and older patients except for Test Day 4 in the bitolterol-treated patients (2.3 hours versus 4.1 hours, $p < 0.05$). This shorter duration of action corresponded with the higher mean baseline FEV₁ on Test Day 4 in the younger age group (Table 2).

Increases in FEF_{25%–75%} above baseline were parallel to those obtained with FEV₁. Approximately 90% of patients had greater than 15% increases with both medications on all test days. Mean maximum increases in FEF_{25%–75%} in the bitolterol and isoproterenol groups were 85% and 82% above baseline, respectively.

The mean number of sprays used was close to the six sprays per day that were prescribed. There was little fluctuation in the dose of theophylline that was taken by 74% and 77% of patients in the two medication groups, respectively. Serum theophylline levels assayed at 120 minutes after treatment with the study medications were $< 5 \mu\text{g/ml}$ in more than 90% of patients, indicating that doses were withheld before the test days.

“Bursts” of oral prednisone in excess of the maximum permitted dose of 10 mg of prednisone q.o.d. were required by 23 bitolterol patients and 33 isoproterenol patients to treat exacerbations

TABLE 4. MEDIAN DURATION OF ACTION (HOURS)^a

Treatment	Test day			
	1	2	3	4
Bitolterol				
n ^b	95	94	90	92
4–8 years	3.7	4.7	3.8	2.3
9–12 years	4.8	4.2	3.6	4.1
all	4.4	4.3	3.7	3.1
Isoproterenol				
n ^b	100	82	72	76
4–8 years	1.5	1.6	1.7	1.2
9–12 years	1.1	2.0	1.5	2.4
all	1.2	1.7	1.6	2.2
Bitolterol vs. Isoproterenol				
p =	0.001	0.002	0.008	0.066

^aIncrease in FEV₁ $> 15\%$ above baseline.

^bNumber of patients evaluated for duration of increase in FEV₁ $\geq 15\%$ above baseline on each test day.

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TABLE 5. PATIENT WITHDRAWAL

<i>Reason</i>	<i>Bitolterol</i>	<i>Isoproterenol</i>
Lack of efficacy	5	11
Side effects	1	3
Lack of efficacy and side effects	0	2
Exacerbation of asthma	0	2
Noncompliance	4	3
Menarche	2	0
Total	12	21

of asthma. The mean baseline FEV₁ was lower in the steroid-using patients than in those not taking steroids, consistent with more severe asthma in the former. There were no significant differences in increase in FEV₁ or in duration of bronchodilation in steroid-taking patients by comparison with those not taking steroids.

The reasons for patient withdrawal from the study are presented in Table 5. Overall, more isoproterenol-treated patients withdrew from the study on account of lack of efficacy and/or undesirable side effects. All complaints of adverse effects are given in Table 6. These were generally mild and of short duration. There were no significant laboratory or ECG abnormalities that were considered treatment related.

TABLE 6. ADVERSE EFFECTS

	<i>Bitolterol</i> (<i>n</i> = 121)	<i>Isoproterenol</i> (<i>n</i> = 121)
Tremor	6 (5.0%)	3 (2.5%)
Headache	4 (3.3%)	6 (5.0%)
Nervous/restless	2 (1.7%)	2 (1.7%)
Tachycardia	4 (3.3%)	2 (1.7%)
Mouth/throat irritation	2 (1.7%)	2 (1.7%)

DISCUSSION

This study demonstrates that bitolterol used regularly on a daily basis for 3 months by MDI was a safe and effective bronchodilator in asthmatic children aged 4–12 years. Mean maximum increase in FEV₁ above baseline values ranged from 31.3% to 34.7% with bitolterol and was very similar to the maximum values obtained with isoproterenol. By comparison, mean maximum percent increases in FEV₁ above baseline during a 6-week study of repetitive dosing with bitolterol by MDI in adults ranged from 22.3% to 29.3% in one study⁽³⁾ to 35–40% in other studies of patients with similar mean baseline FEV₁.^(4,5)

In this study, as in the investigations in adults, bitolterol had a significantly longer duration of action than isoproterenol. Median duration of increase in FEV₁ >15% above baseline ranged from 3.1 to 4.4 hours with bitolterol in these children. In the adult studies median duration of action was 3 hours to 4.5 hours.^(3–5) In a group of 4 to 12-year-old children, a more clear-cut dose-related response was obtained in children over 7 years of age but overall the mean duration of bronchodilation was 3.5–4.5 hours.⁽⁶⁾ In all adult and pediatric investigations of bitolterol MDI reported, some patients had bronchodilation with >15% increase in FEV₁ for more than 8 hours after treatment.

Bronchodilator aerosols by MDI are efficacious, convenient, and safe. This method of delivery is recommended for the treatment of asthma by those patients able to use it because of the direct action of the medication in the lungs with minimal side effects.⁽⁸⁻¹⁰⁾ There is a general perception that children are unable to use MDI, but the age at which coordination is adequate for optimal use is not clear. Although the published studies of β -agonist bronchodilators by MDI in children are difficult to compare because of the different age ranges evaluated and other variables, there is ample evidence that they are effective in children.^(11,12) For example, in 10 children ages 5–13 years a single inhalation of both salbutamol (100 μ g) and isoproterenol (100 μ g) induced similar mean increases in FEV₁ above baseline of approximately 30%, and in the case of albuterol no significant decline was observed 2 hours after treatment.⁽¹³⁾ In a similar study in 16 children 7–13 years of age treated with fenoterol (200 μ g) or salbutamol (100 μ g), increase in FEV₁ >15% above baseline was still evident 6 hours after treatment.⁽¹⁴⁾ Fenoterol administered by MDI gave significant improvement in peak expiratory flow rate for more than 5 hours in 13 children 6–12 years old.⁽¹⁵⁾

In several reviews of the use of bronchodilator medications by MDI by asthmatic children with and without inhalation aids the conclusions were that the children with correct technique had no improvement with an inhaler aid.⁽¹⁶⁻¹⁸⁾ Large-volume inhaler aids appeared to be helpful for some children who were unable to learn correct technique. However, because only a fraction of the delivered dose is required to achieve maximal bronchodilation, less than optimal technique may still be sufficient.⁽¹⁶⁾

All studies reported of MDI use by pre-teenage children have been of single-dose treatments; no repetitive dosing evaluations have been published. Investigations of repetitive dosing in young children have been done with oral medication; for example, metaproterenol syrup given continually for 3 months in 6- to 14-year-old children demonstrated efficacy for approximately 3.5–5 hours.^(19,20) Albuterol syrup every 6 hours in 2- to 6-year-old children receiving concomitant theophylline therapy produced significant increases in peak expiratory flow rate for the 2 and 3 hours of observation in two separate 2-week studies.^(21,22) Procaterol syrup and tablet formulations each given every 12 hours for 7 days to children aged 6–12 years produced bronchodilation for 4–6 hours.⁽²³⁾ In no study was there demonstrable subsensitivity.

The study reported here indicated that long-term treatment of asthmatic children with regular tid bitolterol or isoproterenol delivered by MDI produced similar maximum bronchodilation on all test days and this approximated the results reported in adults with these medications.

The duration of action was longer with bitolterol than with isoproterenol in this and all previously published studies. In this study, the lower mean increase in FEV₁ above baseline and the decrease in median duration of bronchodilation that was observed in the 4- to 8-year-old children on Test Day 4 with bitolterol was consistent with the higher mean baseline FEV₁ that they demonstrated on that day (see Table 2). This result is unlikely to be due to tachyphylaxis which would have been manifested by Test Day 2 following 1 month of therapy if it had occurred during the study.^(24,25) Furthermore, no decrease in median duration of bronchodilation was detected in the 9- to 12-year-old bitolterol study group on successive test days. Overall, the isoproterenol-treated patients had lower mean baseline FEV₁ than the bitolterol-treated patients which also lessened the differences between treatment groups. Adverse effects were minor in both treatment groups but the number of children who withdrew from the study on account of lack of efficacy and/or side effects was greater in the isoproterenol-treated group.

We conclude that bitolterol delivered by MDI on a regular basis over a 3-month period appears to be a safe, effective, and well-accepted medication for children with moderate to moderately severe asthma. There is a need for additional long-term studies in asthmatic children using the MDI for delivery of bronchodilator medication.

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