Dose-response Study of Nebulized Bitolterol Mesylate Solution in Asthmatic Patients*

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Bitolterol mesylate, a new beta₂ adrenergic bronchodilator, is a "pro-drug" which is activated by esterases in the lung. In order to determine the optimal bronchodilator dose of bitolterol, six doses, (0.5 mg, 1.0 mg, 1.5 mg, 2.0 mg, 2.5 mg, and 3.0 mg), were administered by closed-port, intermittent-flow nebulization (CPIF) to asthmatic patients on different days. For most patients, the onset of bronchodilator activity (FEV₁, increase of at least 15 percent above baseline) occurred within 5 minutes and lasted at least 8 hours. Maximum mean increases in FEV₁ were 46-50 percent at the 1.0 mg to 3.0 mg doses. Beyond the 1.0 mg dose, there was no significant improvement in bronchodilator effect, but adverse effects, particularly tremor, increased at higher doses. The optimal dose of bitolterol administered by CPIF was determined to be 1.0 mg which is similar to the dose of bitolterol recommended for use by metered-dose inhaler (MDI) which is 0.7 mg to 1.1 mg. If continuous-flow nebulization is used, two-three times more drug may be needed for a comparable effect. Bitolterol appears to be a safe, effective and long-lasting bronchodilator when administered by jet nebulization.

Investigators have worked for years to develop beta₂ adrenergic bronchodilator drugs with increasing beta₂ specificity, longer durations of action, and reduced cardiac effects. Lands et al described structural differences in various catecholamines which provided different adrenergic responses, classified as alpha, beta, and beta₂, thereby providing the groundwork in the search for compounds with increased beta₂ specificity.

Although no pure pulmonary or beta₂ selective compound has been found, a number of compounds with enhanced beta₂ adrenergic activity have been synthesized. One of these compounds, bitolterol, differs from isoproterenol by esterification of the catechol hydroxy groups and the addition of a third methyl group to the terminal amino group. Bitolterol is a "pro-drug" which is metabolized by esterase hydrolysis to release the active catecholamine, colterol (n-t-butylarterenol) (Fig 1).1,3

In animal studies, bitolterol demonstrated prolonged bronchodilator action and reduced cardiovascular effects.4 Comparison of the activities of bitolterol and isoproterenol, administered in aerosolized form to dogs, revealed longer-lasting activity for bitolterol. At equibronchodilator doses, bitolterol had approximately 1/10 the chronotropic effect and 1/13 the inotropic effects of isoproterenol. Cockcroft et al5 compared bronchodilator effects of inhaled bitolterol to inhaled metaproterenol in ten asthmatic patients and showed that bitolterol is an effective bronchodilator drug with efficacy and duration of action at least as great as metaproterenol.

In the present study, we evaluated the bronchodilator effects and adverse effects of bitolterol in order to determine the optimal dose of bitolterol

![Figure 1. Structure of bitolterol and colterol.](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21558/ on 04/08/2017)
administered through a patient-actuated, closed-port, intermittent flow nebulization system (CPIF) for 15 minute periods to patients with bronchial asthma.

**Material and Methods**

Thirty patients with bronchial asthma (23 males and seven females) were studied at three study centers. The age range was 13 to 60 years, and the mean age was 26.3 years. Patients with coexisting cardiac, pulmonary, renal, hepatic, endocrine or central nervous system diseases, as well as women of child-bearing potential, were excluded from the study. Patients were not using steroids and were not steroid-dependent. The prior drug status of the patients studied were as follows: 90 percent were using aerosolized bronchodilators (82 percent of these patients were also using theophylline), 7 percent were receiving theophylline alone and 3 percent were using only an oral beta-agonist bronchodilator. Pretreatment FEV₁, values ranged from 40-70 percent of predicted normal values. Each patient had at least 15 percent improvement above baseline FEV₁, following two inhalations of isoproterenol hydrochloride (262 μg) from a commercial metered-dose inhaler (MDI), isoproterenol (Isuprel) mistmeter. Informed consent was obtained and the study was approved by the Institutional Review Boards at the three study sites.

Patients did not take cromolyn sodium for at least two weeks, or steroids for at least one month, prior to entering or during the study. Aerosolized beta-adrenergic agonists were also excluded for a minimum of 12 hours prior to each study treatment. Patients did not take theophylline for at least 12 hours or long-acting theophylline preparations for at least 24 hours prior to study treatments.

**Study Design**

Thirty patients received sequentially administered single treatments with increasing doses of bitolterol mesylate solution on different study days three to seven days apart as follows: 0.5 mg, 1.0 mg, 1.5 mg, 2.0 mg, and 2.5 mg, via CPIF. A 3.0 mg dose was terminated after administration to ten patients because of a high incidence of tremor. Isoproterenol was administered by CPIF to 29 patients, of whom two received 1.0 mg, 19 received 1.5 mg, and eight received 2.0 mg dose. Five study patients also received placebo treatments consisting of diluent alone. The CPIF (DeVilbiss nebulizer No 645, DeVilbiss Co, Somerset, PA) (Fig 2), had an inhalation port but no exhalation port so that, when driven by a compressor (Pulmo-side, DeVilbiss No 561547), aerosol was not generated into the environment during drug administration. The output of the compressor was 12 liters per minute and at this flow rate the nebulized particles have a mass median diameter less than 5 μm.

On treatment days each patient received nebulized medication throughout a 15-minute period which ended before 10 A.M. Medication was placed in the nebulizer along with diluent to produce a total volume of 2.0 ml. Nebulizers were weighed before and after treatment to estimate the efficiency of drug delivery. Lung spirometry, respiratory rate, pulse rate and blood pressure were measured at 30 and 15 minutes prior to treatments, immediately before treatment, and at 5, 15, 30, 60, 90, 120, 180, 240, 320, 360, 420 and 480 minutes after each treatment. Electrocardiographic tracings were taken at 30 minutes prior to treatments and at 30, 60 and 240 minutes after each treatment.

Maximum percentage of improvement over baseline in FEV₁ was analyzed by a two-way analysis of covariance with patients and treatment effects and baseline percent predicted normal FEV₁ as a covariate. The duration of FEV₁ action was defined for each patient as the length of time during which the FEV₁ was increased by 15 percent or more over the baseline.

**Results**

Baseline FEV₁ values for the bitolterol- and isoproterenol-treated groups were similar (Table 1). Greater than 80 percent of patients had responded to bitolterol or isoproterenol within 5 minutes after completing treatments. Following treatments with 0.5 mg of bitolterol, 87 percent of the patients responded within 90 minutes, and at higher doses (1.0 mg to 3.0 mg) 93-100 percent of the patients responded. Following treatment with isoproterenol, all patients, except for one treated with 1.5 mg, responded within 90 minutes. Peak bronchodilator effect occurred within 90 minutes for all doses of bitolterol and at 5 minutes following isoproterenol.

Maximum mean improvements from baseline FEV₁,

<table>
<thead>
<tr>
<th>Table 1—Mean Baseline FEV₁ (L) and Mean of Predicted FEV₁, By Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dose (mg)</strong></td>
</tr>
<tr>
<td><strong>No. Patients</strong></td>
</tr>
<tr>
<td><strong>Mean Baseline FEV₁ (L)</strong></td>
</tr>
<tr>
<td><strong>Mean of % Predicted FEV₁</strong></td>
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</tbody>
</table>

Nebulized Bitotrol Mesylate in Asthma (Pinnas et al)
Mean Percent Improvement In FEV\textsubscript{1} From Baseline

**Bitolterol**
- 0.5 mg (n = 30)
- 1.0 mg (n = 30)
- 1.5 mg (n = 30)
- 2.0 mg (n = 30)
- 2.5 mg (n = 29)
- 3.0 mg (n = 10)

**Isoproterenol**
- 1.5 mg (n = 19)
- 2.0 mg (n = 8)

**Figure 3.** Mean percentage of change from baseline FEV\textsubscript{1} by dose and time. **Upper:** bitolterol, and **lower:** isoproterenol.

were 38 percent, 46 percent, 48 percent, 49 percent, 50 percent following 0.5 mg, 1.0 mg, 1.5 mg, 2.0 mg, 2.5 mg and 3.0 mg of bitolterol respectively (Fig 3a). A dose-response effect, while relatively flat, was statistically significant (p<0.001). For isoproterenol the maximum mean improvements from baseline FEV\textsubscript{1} were 25 percent, 46 percent and 51 percent following 1.0 mg, 1.5 mg and 2.0 mg doses, respectively (Fig 3b). The overall mean change in FEV\textsubscript{1} was greater than 15 percent above baseline throughout the eight-hour observation period for all dosages of nebulized bitolterol (0.5 mg to 3.0 mg). The median duration of action for bitolterol was greater than eight hours for all doses compared to 6½ hours or less for isoproterenol and at least three-fourths of responding patients had durations of action greater than five hours for bitolterol compared to less than two hours for isoproterenol treatments.

As a measure of residual solution remaining in the nebulizers following completion of treatments, nebulizers were weighed before and after treatments. The mean amount of solution nebulized was 1.43 ± 0.22 g (mean ± standard deviation), which is 71.5 percent of the 2.0 ml originally placed in the nebulizer.

**Cardiovascular Effects**

Pulse rate increases of at least 15 beats/min during treatment and for four hours after treatment are shown in Table 2. The incidence of pulse rate increases of at least 15 beats/min was relatively low, 3 to 10 percent, following 0.5 mg to 1.5 mg of nebulized bitolterol, and 5 and 13 percent following 1.5 mg and 2.0 mg isoproterenol treatments, respectively. The incidence of pulse rate increases was higher during isoproterenol than during bitolterol treatments (Fig 4). Pulse rates...
returned to baseline within an hour for 2.0 mg and 2.5 mg and within 1.5 hours following the 3.0 mg dose. Mean pulse rates for the five patients treated with placebo were also increased with a mean maximum of 7.8 beats/min during the observation periods, presumably related to lack of improvement in pulmonary function in this group.

Mean systolic blood pressure remained less than 120 mm Hg following all treatments with bitolterol at doses of 0.5 mg to 2.5 mg and following 1.5 mg of isoproterenol. For ten patients who received 3.0 mg of bitolterol, the mean systolic blood pressure increased from 117 mm Hg to 131 mm Hg within five minutes following completion of treatments and remained slightly elevated during the four hours following treatments. A similar increase in mean systolic blood pressure, from 118 mm Hg to 128 mm Hg, was observed in eight patients who received 2 mg of isoproterenol. The mean diastolic blood pressure remained less than 80 mm Hg after all treatments with bitolterol and isoproterenol, changing minimally from baseline. At the highest doses, two patients had significant elevations in blood pressure, one treated with 3.0 mg of bitolterol who showed a rise in systolic blood pressure of 50 mm Hg and one who received 2.0 mg of isoproterenol who had a rise of 65 mm Hg.

The blood pressure changes observed for bitolterol at 0.5 mg to 2.5 mg doses and for isoproterenol at the 1.5 mg dose were not considered to be clinically significant.

Electrocardiographic findings remained normal throughout the study except for four patients with ECG changes at 30 minutes following administration of bitolterol which consisted of nonspecific flattening of

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**Table 2—Number of Patients with Pulse Rate Increases**

<table>
<thead>
<tr>
<th>Increase (beats/min)</th>
<th>Placebo</th>
<th>Bitolterol</th>
<th>Isoproterenol</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=5</td>
<td>0.5 mg</td>
<td>1.0 mg</td>
</tr>
<tr>
<td><strong>Following Completion of Treatments (First Four Hours)</strong></td>
<td>30</td>
<td>(30)</td>
<td>(30)</td>
</tr>
<tr>
<td>15-20</td>
<td>1</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>21-30</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>31-40</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>During Treatments</strong></td>
<td>(N)=2</td>
<td>(18)</td>
<td>(19)</td>
</tr>
<tr>
<td>15-20</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>21-30</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>31-40</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

*Vital signs were monitored during the 15 to 20 minute treatment periods in the number of patients indicated (N) and maximum increases after and during treatments were analyzed separately.
T waves and minimal prolongation of the QT interval. Palpitations occurred in two patients treated with bitolterol, but only at the 3.0 mg dose.

**Other Adverse Effects**

Treatments with 0.5 mg, 1.0 mg and 1.5 mg of bitolterol were well tolerated and produced few adverse effects. The most frequent side effect was a mild, transient tremor which usually lasted less than one hour. The incidence of tremor demonstrated a greater dose relationship than the increases in peak bronchodilator effect (Fig 5). Tremor incidence ranged from 3 to 60 percent for the six bitolterol treatments of 0.5 mg to 3.0 mg. For isoproterenol, the tremor incidence was also dose-related, rising more abruptly with increased dosage, ie, 11 and 75 percent following 1.5 mg and 2.0 mg treatments, respectively. One of two patients treated with 1.0 mg of isoproterenol also experienced tremor (Table 3).

Mild, transient chest discomfort was noted by three patients during one or more treatments with bitolterol and was considered to be respiratory rather than cardiac in origin by the investigators. In a few patients, other adverse effects occurred which were also mild and transient and these included vertigo, dizziness, lightheadedness, headache and nervousness. Since these adverse effects were observed only in one or two patients at each dose and were also observed in placebo-treated patients, hyperventilation in these patients during the inhalation procedure may have played a role (Table 3). The total number of patients who reported one or more adverse effects increased from 37 to 57 percent as the dose of bitolterol was increased from 1.5 mg to 2.0 mg. For isoproterenol, the number of patients who had one or more adverse effects increased from 16 to 88 percent as the dose was increased from 1.5 mg to 2.0 mg.

**DISCUSSION**

This dose-response study was undertaken to determine bronchodilator dose and margin of safety for bitolterol and isoproterenol aerosols administered via CPIF. Previous studies have demonstrated that the duration of action of bitolterol is greater than isoproterenol when administered by metered-dose inhaler.\(^6,7\) Our results with CPIF support these findings.

Using CPIF, all doses of bitolterol provided rapid bronchodilation although 1.0 mg of bitolterol was the optimal dose which provided adequate bronchodilation with few untoward effects. In other studies, the amount of drug reaching the patient depends upon many factors including nebulizer used, the amount of diluent and whether flow is continuous or intermittent.\(^8,9\) Furthermore, Shim and Williams\(^10\) reported that 53-63 percent of the solution placed in the nebulizer was nebulized and Kradjan and Lakshminary\(^11\) found that 53-72 percent was nebulized. Clay et al,\(^12\) studying various fill volumes, measured 35-65 percent release of aerosol with 2 ml, 60-80 percent release with 4 ml, and 70-85 percent release with 6 ml fill volume. In the present study, in spite of a 2.0 ml fill volume, factors such as the characteristics of the nebulizer, flow rate and careful administration led to reasonably efficient nebulization, ie, a 72 percent release of aerosol. Also, during nebulization the drug in solution may become more concentrated so that less drug may actually be nebulized than nebulizer weight calculations would predict.\(^13\) The recommended dose of bitolterol administered by MDI is 0.7 mg to 1.1 mg,\(^7\) which is in the same range as the optimal dose determined in the present study for CPIF therapy. Administration of 2.5 mg of isoproterenol hydrochloride is recommended by the package insert, but one should be aware that this recommendation was based upon a continuous-flow, open-port nebulizer, and that 2.0 mg had an unacceptably high incidence of side effects in the present study. Drug delivery by CPIF is substantially greater than the open-port continuous-flow nebulizer system which requires two-three times more drug for comparable bronchodilator effect.\(^9,14\) Kemp et

**Table 3—Incidence of Adverse Effects**

<table>
<thead>
<tr>
<th>Adverse Effect</th>
<th>Placebo 0.5 mg</th>
<th>Placebo 1.0 mg</th>
<th>Placebo 1.5 mg</th>
<th>Placebo 2.0 mg</th>
<th>Placebo 2.0 mg</th>
<th>Bitolterol 1.5 mg</th>
<th>Bitolterol 2.0 mg</th>
<th>Isoproterenol 1.5 mg</th>
<th>Isoproterenol 2.0 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>5 (40)*</td>
<td>30 (27)</td>
<td>30 (27)</td>
<td>30 (37)</td>
<td>30 (57)</td>
<td>29 (48)</td>
<td>19 (16)</td>
<td>8 (88)</td>
<td></td>
</tr>
<tr>
<td>Tremor</td>
<td>0 (0)†</td>
<td>1 (3)</td>
<td>3 (10)</td>
<td>6 (20)</td>
<td>11 (37)</td>
<td>10 (35)</td>
<td>6 (60)</td>
<td>2 (11)</td>
<td>6 (75)</td>
</tr>
<tr>
<td>Lightheadedness</td>
<td>0 (0)</td>
<td>2 (7)</td>
<td>3 (10)</td>
<td>3 (10)</td>
<td>1 (3)</td>
<td>4 (13)</td>
<td>3 (30)</td>
<td>0 (0)</td>
<td>2 (25)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>1 (20)</td>
<td>3 (10)</td>
<td>2 (7)</td>
<td>0 (0)</td>
<td>2 (7)</td>
<td>2 (7)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>2 (25)</td>
</tr>
<tr>
<td>Vertigo</td>
<td>1 (20)</td>
<td>1 (3)</td>
<td>1 (3)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1 (10)</td>
</tr>
<tr>
<td>Headache</td>
<td>0 (0)</td>
<td>1 (3)</td>
<td>0 (0)</td>
<td>2 (7)</td>
<td>0 (0)</td>
<td>1 (3)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1 (12)</td>
</tr>
<tr>
<td>Nervousness</td>
<td>0 (0)</td>
<td>1 (3)</td>
<td>0 (0)</td>
<td>2 (7)</td>
<td>0 (0)</td>
<td>1 (3)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1 (12)</td>
</tr>
<tr>
<td>Chest Discomfort</td>
<td>0 (0)</td>
<td>1 (3)</td>
<td>1 (3)</td>
<td>1 (3)</td>
<td>1 (3)</td>
<td>1 (3)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1 (12)</td>
</tr>
<tr>
<td>Palpitations</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>2 (20)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

*Number of patients studied (percentage of patients with one or more adverse effects)
†Number of patients with adverse effects (percentage of patients studied)
al compared bitolterol 1.0 mg, by CPIF to continuous-flow nebulization and found the optimal dose to be 2.5 mg in the latter system. Physicians should be aware of this difference and use smaller doses for CPIF than for continuous-flow nebulization. The use of additional diluent and breathing after each inhalation can further enhance CPIF therapy and deliver more drug to the patient.

Bronchodilator effect observed in the present study was sustained for bitolterol, *ie*, following 1.0 mg of bitolterol, the mean increase in FEV₁ was approximately 20 percent above baseline at eight hours after treatments. The prolonged duration of action of bitolterol may be due to certain structural and metabolic features of the drug. Two ester groups of bitolterol protect the drug from rapid biodegradation by catechol-o-methyl transferase and an additional methyl group, an N-alkyl substituent in colterol, the active metabolite of bitolterol, decreases its susceptibility to the action of monoamine oxidase. The high liposolubility of bitolterol ⁴ ⁵ and the slow release of active compound by lung esterases also contribute to prolong its duration of action.

Kass and Mingo ⁶ reported an increase above baseline in FEV₁ of 32.8 percent which had peaked at two hours following administration of 0.7 mg of bitolterol by MDI and had decreased to 9.8 percent at eight hours. In another study, the peak mean increase was 30.7 percent in FEV₁ within one hour following the same dose of bitolterol by MDI. ⁷ In the present study, following 1.0 mg of bitolterol administered via CPIF, peak mean response, measured as mean change in FEV₁ above baseline, was 43.1 percent at 30 minutes following treatment. Our more favorable response may result from one or more of several factors: 1) a greater dose actually reaching the patient, 2) better distribution of drug within the lung, and 3) patient variability. Other evidence that nebulization can produce a greater response than MDI was presented by Tarala et al ⁸ who reported that nebulized albuterol produced further improvement in pulmonary function following maximal bronchodilation by MDI.

Analysis of the cardiac and pulmonary effects of bitolterol revealed that relatively few cardiac effects were observed at doses which produced adequate bronchodilator effect. There were no significant adverse cardiac effects during the study and there was a lower incidence of pulse rate increases of at least 15 beats per minute during treatments with bitolterol than was observed with isoproterenol treatments (Table 3). Greater drug effect in lung compared to heart may be attributable to the observations that lung has greater affinity for bitolterol ⁴ ⁵ and also more esterase activity than heart. ⁴ ⁵ The inhaled route delivers drug directly to the beta₂ adrenergic receptors, thereby further reducing the stimulation of beta receptors.

Except in severe asthma when severe obstruction or mucous plugs may be present, beta-agonists are most effective by the aerosol route. ⁹ ¹⁰ Inhaled bronchodilators, at lower doses, have more rapid onset, greater bronchodilator effect and fewer untoward effects than oral drugs. ⁸ ¹ⁱ However, Paterson et al ⁸ found that 43 percent of isoproterenol could be recovered from the mouth after inhalation. Rinsing the oropharynx following aerosol therapy and the use of spacers may reduce systemic absorption and side effects of inhaled bronchodilators. Since less drug enters the systemic circulation by the aerosol than by the oral route, aerosol therapy is commonly associated with a reduced incidence of untoward cardiovascular effects. Shim and Williams ⁹ ¹⁰ demonstrated that proper inhalation of an aerosolized bronchodilator over an adequate period of time enhances bronchodilation presumably by permitting the drug to progressively reach parts of the airway which were previously obstructed.

In summary, bitolterol was found to be a safe and effective bronchodilator with a prolonged duration of action. One milligram of bitolterol administered via CPIF provided bronchodilator activity usually for eight hours with an adequate margin of safety.

**References**


20 Paterson JV, Conolly ME, Davies DS, Dollery CT. Isoprenaline resistance and the use of pressurized aerosols in asthma. Lancet 1968; 2:426-29