Original Article

# Role of Bambuterol in the Management of Bronchial Asthma

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## Abstract

**Background:** Asthma is a long-term inflammatory disorder of the airways characterized by wheezing, dyspnea, and cough. For the last few decades, inhalational devices have been used in the management of the disease, but compliance remains the problem. Higher doses of oral medications used with prominent side effects precluded the use of oral beta-agonist bronchodilators, and the search for an ideal beta-adrenergic bronchodilator continues. This study was conducted for evaluation of the role of oral bambuterol in the management of bronchial asthma. **Aims and Objectives:** Our study aimed to evaluate the potency and effectiveness of oral bambuterol in the management of the disease in fifty patients followed up over 2 weeks with objective assessment of symptom scores and changes in the frequency of rescue bronchodilator after 2 weeks of treatment. Side effects, if any, were documented for all patients. **Methods:** The study was conducted on fifty patients with chronic bronchial asthma. They were given 10 mg of bambuterol once daily orally for 14 days. Pulmonary function tests were performed at days 1, 7, and 14. Forced vital capacity (FVC), forced expiratory volume in 1 s ($FEV_1$), and peak expiratory flow rate (PEFR) were measured. Patients were assessed for symptom score and side effects at days 1, 7, and 14. **Results:** After completion of the study, significant improvement in the symptom score, FVC, $FEV_1$, and PEFR was obtained with minimal side effects. **Conclusion:** Bambuterol 10 mg oral tablet once a day provides significant improvement in pulmonary function tests and effectively reduces asthmatic symptoms with minimal side effects.

**Keywords:** Asthma, bambuterol, pulmonary function tests, symptom score

## Introduction

Asthma is a disorder caused by airway hyperresponsiveness to various allergens. It involves interaction between bronchial hyperreactivity and airflow obstruction. This interaction varies among and within patients over time.[1] There occurs inflammation of the airways which affects both the airway caliber and airflow, causing bronchospasm.[2] Due to notable increase in the disease incidence, many new developments have been done to enhance the knowledge of pathophysiology of this disease, which results in episodic exacerbation of airway dysfunction, increased secretions, cough, and other symptoms.[3] The pharmacotherapy of asthma helps to control both inflammation and spasm of bronchi. Corticosteroids and β2-agonists are presently being used for the treatment, via inhalational route. Conventional β2-adrenergic agonists act for shorter duration. The effect of newer bronchodilators is not more than 12 h.[4,5] Bambuterol is a long-acting β-adrenoceptor agonist having longer duration of action. It is used in the treatment of asthma. It stimulates through β2-adrenergic receptors of intracellular adenylate cyclase (an enzyme which converts adenosine triphosphate into cyclic adenosine monophosphate [AMP]). Cyclic AMP promotes relaxation of smooth muscles of bronchus and inhibits release of mediators from primed mast cells.[6,7] It is an inactive prodrug of terbutaline, which is an agonist of β2-receptor. It undergoes oxidation and hydrolysis, mediated via butyrylcholinesterase, and is transformed into terbutaline.[8,9] Bambuterol reversibly inhibits plasma cholinesterase in a dose-dependent manner, so the metabolism of its prodrug occurs in a slow and controlled fashion throughout the entire 24 h.[10,11] Therefore, it works as an endogenous reservoir of terbutaline, allowing it to be used once daily.[12,13]

Thus, the clinical efficacy of once-daily bambuterol is almost equivalent to twice-daily sustained-release terbutaline.[14] The pharmacokinetics of bambuterol and terbutaline in healthy controls was studied by Nyberg *et al*.;[15] the total clearance of bambuterol administered intravenously was 1.25 l $min^{-1}$, 10%

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of which was of renal origin. After oral intake of bambuterol, terbutaline was released slowly for a longer duration which was confirmed by the flat profile of the plasma concentration versus time profile of terbutaline which was rather flat after the oral administration of bambuterol, thus favoring its once-daily administration.

Bambuterol has less side effects and similar clinical efficacy to other oral bronchodilators.[16] The low frequency of side effects is explained by the smooth and sustained plasma levels of terbutaline released at a steady state.[17] Other side effects include headache, tonic muscle cramps, and palpitations. These effects are dose dependent and majority of these reverse spontaneously within the first 1–2 weeks as found by Persson *et al*.[18]

### Aims and objectives

1. To study the efficacy of oral bambuterol in the management of bronchial asthma
2. To study the improvement in symptom scores and any side effects after 2 weeks of therapy
3. To study the frequency of rescue bronchodilator used after 2 weeks of treatment.

## Methods

This study was conducted on fifty patients suffering from chronic asthma attending the outpatient department of Department of TB and Respiratory Diseases, Sri Guru Ram Das Institute of Medical Sciences and Research, Amritsar, Punjab, India. The study comprised of both male and female patients with age ranging from 18 to 60 years. Patients having acute severe asthma were excluded from the study. Apart from a history of episodic breathlessness, cough, wheezing, and expectoration, a history of atopy or other allergy was also documented.

Inclusion criteria comprised of patients having reversible airway obstruction, i.e., >12% reversibility and 200 ml of forced expiratory volume in 1 s ($FEV_1$) after 2 puffs of salbutamol inhaler (100 μg/puff) in the absence of any chest infection.

Exclusion criteria comprised of irreversible airway obstruction, chronic bronchitis, cor pulmonale, ischemic heart disease, impaired hepatic and renal functions, tuberculosis, and pregnant and lactating women.

Selected patients were given a single dose of oral bambuterol 10 mg at evening time for 14 days with salbutamol inhaler as rescue inhaler. All the other bronchodilators were discontinued at least 48 h prior to the start of oral bambuterol, but those receiving oral steroids were allowed to continue.

Pulmonary function tests were done in each case at the start of therapy, i.e., day 1 and then at days 7 and 14. Upon performing spirometry, $FEV_1$, forced vital capacity (FVC), and peak expiratory flow rate (PEFR) were documented.

The percentage reversibility in $FEV_1$ was calculated by repeating the $FEV_1$, 15 min after two puffs of salbutamol (100 μg/puff).

These tests were done using a computerized spirometer (Ndd Medical Technologies) which also gave the predicted values of $FEV_1$, FVC, and PEFR as well as percentage of these values of each patient scaled to patient's height, weight, age, gender, and environmental temperature. The predicted values were based on European Respiratory Society/European Society of Cardiology for adult patients, i.e., >17 years. The patients were asked to follow up at days 7 and 14. Any side effects of oral bambuterol such as headache, tremor, palpitation, or tachycardia were documented.

Symptom scores at the start of therapy and at days 7 and 14 were noted to assess the subjective improvement.

The asthmatic symptoms were graded as follows:

- 0: No symptoms
- 1: Mild symptoms (i.e., patient is able to do his/her routine work despite the presence of symptoms without any difficulty, expiratory wheeze, decreased air entry at bases, and $SpO_2$ 90%–93%)
- 2: Moderate symptoms (i.e., patient is able to do his/her routine work but with some difficulty and sleep is disturbed due to these symptoms, suprasternal indrawing, scalene retractions, both inspiratory and expiratory wheeze, widespread decrease in air entry, and $SpO_2$ <90%)
- 3: Severe symptoms (i.e., patient is unable to do work and sleep is disturbed, audible without stethoscope/silent chest with minimal air entry and absent/minimal air entry).

### Statistical analysis

Paired Student's *t*-test was used to interpret the data. $P < 0.05$ was considered statistically significant and $P < 0.001$ as highly significant. Mean and standard deviation were calculated wherever required.

## Results

In this study, bambuterol, a prodrug of β2 agonist terbutaline, was evaluated in the management of asthma. It was found that there were 28 (56%) males and 22 (44%) females. Majority of the cases were seen in the age group of 18–25 years (36%) [Table 1].

Twenty-six patients (52%) had a history of atopy and nasal allergy. Out of these, 10 were males and 16 were females [Table 2].

Family history of asthma was observed in 20 (40%) cases [Table 3].

There was a significant increase in mean percentage $FEV_1$ values at day 7 and day 14 from the basal percentage values by 20% and 33%, respectively [Table 4].

A significant improvement in mean percentage value of FVC by 16% and 28% was noticed at days 7 and 14, respectively [Table 5].

Similarly, there was also significant increase in mean percentage PEFR from basal percentage value by 13% and 22% by days 7 and 14, respectively [Table 6].

The symptom score decreased from 7.36 ± 1.80 at day 1 to 3.80 ± 1.87 at day 7 and 1.08 ± 1.07 at day 14 [Table 7].

Drug was well tolerated by most of the patients. Mild headache was reported in 12 patients and tremors in four patients [Table 8].

The mean frequency of rescue bronchodilator decreased from 3.06 puffs/day for each patient at day 7 to 1.1 puffs/day for each patient at day 14 [Table 9].

## Discussion

Bambuterol, the prodrug of terbutaline, improves airflow status over 24 h when administered once daily in the evening. Bambuterol when given in the evening resulted in a statistically significant increase in $FEV_1$, FVC, and PEFR. The frequency of asthma symptoms declined at the end of this study. The main objectives of asthma treatment are to control symptoms and maintain near-normal pulmonary function and normal physical activity.[17,19]

In this study, there was a significant increase in $FEV_1$, FVC, and PEFR values on days 7 and 14 after treatment with oral bambuterol. Furthermore, the mean symptom score decreased to 3.80 ± 1.87 on day 7 and to 1.80 ± 1.07 on day 14. Persson *et al*.[18] also reported that 10 mg bambuterol when given orally acts effectively for 24 h. This is depicted as an increase in mean daily morning and evening PEFR (11 L/min, adjusted means) throughout the study, as compared with placebo. Persson *et al*.[18] found that mean baseline $FEV_1$ and $FEV_1$% of predicted values were 2.05 L and 62%, respectively. In this study, it was found that the total number of rescue bronchodilator puffs was also reduced. These findings were consistent with the findings of Petrie *et al*.[20] who reported a 16% increase in mean PEFR on awaking and 10% improvement in evening PEFR measured 24 h after bambuterol 20 mg intake.

**Table 1: Age and sex distribution**

| Age groups (years) | Male | Female | Total (%) |
|---|---|---|---|
| <25 | 10 | 8 | 18 (36) |
| 26-35 | 2 | 6 | 8 (16) |
| 36-45 | 8 | 8 | 16 (32) |
| 46-55 | 4 | | 4 (8) |
| 56-60 | 4 | | 4 (8) |
| Total (%) | 28 (56) | 22 (44) | 50 (100) |

**Table 2: History of atopy and allergy**

| Sex | Number of patients (%) |
|---|---|
| Males | 10 (20) |
| Females | 16 (32) |
| Total | 26 (52) |

**Table 3: Family history of bronchial asthma**

| Sex | Number of patients (%) |
|---|---|
| Males | 12 (24) |
| Females | 8 (16) |
| Total | 20 (40) |

**Table 4: Forced expiratory volume in 1 s (l/s)**

| | Mean | SD | *t* | *P* |
|---|---|---|---|---|
| Predicted | 2.50 | 0.64 | | |
| Basal | 1.08 | 0.36 | | |
| Postsalbutamol | 1.50 | 0.58 | | |
| Day 7 | 1.58 | 0.54 | 3.85 | <0.001 |
| Day 14 | 1.91 | 0.61 | 5.86 | <0.001 |

SD: Standard deviation

**Table 5: Forced vital capacity (l/s)**

| | Mean | SD | *t* | *P* |
|---|---|---|---|---|
| Predicted | 3.02 | 0.68 | | |
| Basal | 1.23 | 0.54 | | |
| Postsalbutamol | 1.61 | 0.59 | | |
| Day 7 | 1.72 | 0.61 | 3.00 | <0.001 |
| Day 14 | 2.07 | 0.68 | 4.97 | <0.001 |

SD: Standard deviation

**Table 6: Peak expiratory flow rate (l/min)**

| | Mean | SD | *t* | *P* |
|---|---|---|---|---|
| Predicted | 459.12 | 88.39 | | |
| Basal | 132.24 | 75.13 | | |
| Postsalbutamol | 175.20 | 70.95 | | |
| Day 7 | 195.60 | 86.79 | 2.77 | <0.05 |
| Day 14 | 235.68 | 80.43 | 4.74 | <0.05 |

SD: Standard deviation

**Table 7: Symptom score**

| | Mean | SD |
|---|---|---|
| Day 1 | 7.36 | 1.80 |
| Day 7 | 3.80 | 1.87 |
| Day 14 | 1.08 | 1.07 |

SD: Standard deviation

**Table 8: Side effects**

| Side effect | Number of patients (%) |
|---|---|
| Mild headache | 12 (24) |
| Tremor | 4 (8) |
| Restlessness and nausea | 2 (4) |

**Table 9: Rescue bronchodilators**

| | Number of puffs | Mean puffs |
|---|---|---|
| 1st week | 1074 | 21.48 |
| 2nd week | 388 | 7.76 |

Frequency of puffs after 1 week: 3.06 puffs/day, Frequency of puffs after 2 weeks: 1.1 puffs/day

In our study, the maximum cases of bronchial asthma were seen in the age group of 18–25 years (36%). Wig *et al*.[21] also found higher incidence of bronchial asthma in younger age group.

Very few adverse effects of bambuterol were reported in the study and no patients withdrew because of them. The frequent complaints were headache, mild tremors, and restlessness. Headache was noticed in 24%, tremors in 8%, and restlessness and nausea in 4% of patients each. These results were similar to those reported by Persson *et al*.[18]

## Conclusion

Bambuterol 10 mg oral tablet once a day provides significant improvement in pulmonary function tests and effectively reduces asthmatic symptoms with minimal side effects. Even after three decades of emphasis on inhalation devices, a considerable population has been observed to not accept them and compliance problems persist. Bambuterol shows a promising role in such asthmatic patients who are noncompliant with inhalation devices or techniques but are willing to adhere to oral therapy. It is in such group of patients that reintroduction of bambuterol fills the missing gap in the management in terms of both results and compliance. Thus, it appears to be ideal for the treatment of asthma.

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### Conflicts of interest

There are no conflicts of interest.

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