



β₂ AGONIST VERSUS CYSTEINYL LEUKOTRIENE RECEPTOR ANTAGONIST IN CHRONIC ASTHMA PATIENTS

Haitham Galal El Din Zakaria*¹ and Mokhles El Nagar²

¹Teaching Assistant at Clinical Pharmacy Department, Faculty of Pharmacy, October 6 University.

²Chest Consultant at Kom Hamada Hospital, El Beheira.

***Corresponding Author: Haitham Galal El Din Zakaria**

Teaching Assistant at Clinical Pharmacy Department, Faculty of Pharmacy, October 6 University.

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ABSTRACT

Background: Asthma is a heterogeneous disease characterised by chronic airway inflammation. Although studies show that control of asthma can be achieved using many drug classes in the majority of patients, surveys repeatedly show that the response is variable due to multifactorial reasons. This study was designed to evaluate the usage of Beta 2 agonist "bambuterol" or Leukotriene receptor antagonist "zafirlukast" as preventive drugs in chronic asthmatics. **Patients and methods:** Using Open-Label clinical trial, 44 patients with moderate persistent asthma were randomly enrolled into 2 groups; the first group contains 22 patients, treated with once daily 10 mg orally bambuterol for 4 weeks and the second group contains 22 patients, treated with twice daily 20 mg orally zafirlukast for 4 weeks. Frequency of asthma symptoms, pulse oximetry (SpO₂) and pulmonary function tests (PFTs) were recorded at baseline and at the end point (after 4 weeks). **Results:** Both bambuterol and zafirlukast showed significant improvement in asthma symptoms, pulmonary function test values and pulse oximetry after 4-week therapy compared to the first visit ($p < 0.05$), however, bambuterol showed more significant improvement in PFT values compared to zafirlukast.

KEYWORDS: Bambuterol; Zafirlukast; Chronic bronchial asthma; Pulse oximetry; Pulmonary function tests.

1. INTRODUCTION

Asthma is a chronic inflammatory disorder arising from not fully understood heterogenic gene-environment interactions. It features variable airway obstruction and bronchial hyper-responsiveness. Clinically, asthmatics exhibit recurrent episodes of wheeze, cough, chest tightness, and shortness of breath.^[1] Although the occurrence of asthma has increased significantly over the last decades in children and adults, major advances have been made in understanding the pathophysiology of this chronic inflammatory disease which leads to episodic worsening of air way function, mucus production, cough and other symptoms.^[2] Cysteinyl leukotrienes (CysLTs) are important mediators of asthma, LTs are eicosanoids derived from arachidonic acid via the 5-lipoxygenase pathway and are produced and released from inflammatory cells such as eosinophils and mast cells and alveolar macrophages.^[3] They induce bronchoconstriction, mucous secretion, increased vascular permeability, and by this way they play one of the important roles in the pathophysiology of asthma.^[4,5,6] Antileukotriene agents, including montelukast, zafirlukast, pranlukast and the 5-lipoxygenase inhibitor zileuton, act by blocking the effects of the cysteinyl leukotrienes.^[7,8] Zafirlukast is a potent oral leukotriene-(C4/E4/D4)-receptors antagonist

approved for the treatment of chronic asthma in patients aged 6 years and older.^[9] Bambuterol is a long acting β₂-adrenoceptor agonist (LABA) used in the treatment of asthma. It is a bis-carbamate ester prodrug of the β₂-adrenoceptor agonist terbutaline. Bambuterol, which is inactive at adrenergic receptors, is converted to terbutaline via oxidation and hydrolysis primarily by butyrylcholinesterase.^[10,11] As other LABAs, bambuterol is used in the long-term management of persistent asthma and should not be utilized as a rescue medication for short-term relief of asthma symptoms. This study was conducted to evaluate the preventive effect of bambuterol or zafirlukast in patients with mild to moderate persistent asthma.

2. PATIENTS AND METHODS

Forty-four patients with moderate persistent asthma were recruited from the Outpatient Clinic at Kom Hamada Specialized Hospital-Al Beheira and divided randomly into two groups 22 patients each. The 1st group: 22 patients, 16 males and 6 females aged 35 ± 10 years, were given bambuterol (Bambec, AstraZeneca) 20 mg orally once daily. The 2nd group: 22 patients, 17 males and 5 females aged 35 ± 10 years were given zafirlukast (Ventair, Delta Pharma) 20mg orally twice daily. All treatments were given for 4 weeks. Moderate persistent

asthma was diagnosed according to the guidelines of the Global Initiative for Asthma and the National Asthma Education and Prevention Program.

Inclusion criteria: (1) Previously diagnosed asthma, (2) Daily asthma symptoms (3) Nocturnal symptoms > 1/week (4) Forced expiratory volume in one second (FEV₁) or peak expiratory flow (PEF) 60-80% predicted values.

Exclusion criteria: (1) History or symptoms of cardiovascular disease, (2) Usage of oral or parenteral corticosteroids within 6 weeks, (3) Pregnancy and (4) Usage of tobacco products within the previous year. (4) Hepatic impairment (5) Alcoholic cirrhosis. The usage of aspirin, warfarin, erythromycin, terfenadine carboxylate and theophylline needs appropriate clinical monitoring during the treatment in zafirlukast group. Also patients continued to take a short-acting inhaled β_2 -agonist as necessary to relieve symptoms. The study protocol was approved by the Research Ethics Committee of Kom Hamada Specialized Hospital. All patients signed written informed consent to participate in the study. The study was performed in a single blind manner. The frequency of asthma symptoms (chest tightness, coughing, night and morning wheeze) were recorded at the beginning and the end of the study for each patient. Pulmonary function tests (PFTs) were also measured at the beginning and at the end of the study using a spirometer with a pneumotachograph sensor (Model ST 90, Fukuda, Sangyo Co., Ltd., Japan). Pulmonary function tests were

performed three times for each subject. The highest level for forced vital capacity (FVC), FEV₁ and PEF were recorded. Baseline and end-point SpO₂ was measured with a Palco Oximeter model 30 (Palco Laboratories, Inc., Santa Cruz, CA, USA). Liver function test was done with Automated analyzer Hitachi 917 was used in the analysis and chemicals were provided by Bio Med EGY-Chem (Cairo, Egypt) at the beginning of the study as well as at its end for patients in zafirlukast group.

Analysis of data

The results were reported as standard error of mean (SEM). Tukey test in comparison with unpaired t-test (2-tailed) was used to compare between treatments groups. The differences between the means are considered significant at the 5% confidence level. The statistical analysis was carried out by using SSPS 15.0. The level of significance was set $p < 0.05$.

3. RESULTS

Asthma symptoms

As demonstrated in Table 1, the mean frequency of asthma symptoms was not significantly different between the bambuterol and the zafirlukast groups at the start of the study ($p > 0.05$). The frequency of all asthma symptoms was significantly reduced in both groups after 4 weeks of treatment ($p < 0.05$). At the study endpoint, the mean monthly frequency of asthma symptoms was significantly reduced in bambuterol group compared to zafirlukast group ($p < 0.05$).

Table 1: Effects of bambuterol and zafirlukast on mean frequency of asthma symptoms.

Asthma symptoms	Bambuterol (n=22)		Zafirlukast (n=22)	
	Baseline	Endpoint	Baseline	Endpoint
Coughing	6.32 $\pm$ 1.78	2.42 $\pm$ 0.59*	6.72 $\pm$ 1.03*	3.15 $\pm$ 0.88*
Night wheeze	9.21 $\pm$ 1.91	2.22 $\pm$ 0.81*	9.85 $\pm$ 2.23*	2.91 $\pm$ 0.75*
Daytime wheeze	10.68 $\pm$ 2.45	6.67 $\pm$ 1.25*	11.19 $\pm$ 2.92*	7.17 $\pm$ 1.74*

*Endpoint values were significantly different from baseline values ($p < 0.05$) in both groups. Data are expressed as means $\pm$ SEM (standard error of the mean). n = Number of patients.

Pulmonary function tests

As shown in Table 2, pre-treatment pulmonary function test (PFT) values were not significantly different between montelukast and bambuterol groups at the start of the study ($p > 0.05$). After 4 weeks of treatment, PFT

values were significantly improved in both zafirlukast and bambuterol patient groups compared to baseline ($p < 0.05$). The improvement in PFT values was more significant with bambuterol compared with zafirlukast.

Table 2: Effects of bambuterol and zafirlukast on pulmonary function tests and pulse oximetry.

Pulmonary Function Tests and Pulse Oximetry	Bambuterol (n=22)		Zafirlukast (n=22)	
	Baseline	Endpoint	Baseline	Endpoint
FVC (L)	2.73 $\pm$ 0.061	3.89 $\pm$ 0.096* ^γ	2.87 $\pm$ 0.085	3.05 $\pm$ 0.056*
FEV ₁ (L)	2.47 $\pm$ 0.055	3.55 $\pm$ 0.092* ^γ	2.61 $\pm$ 0.064	2.46 $\pm$ 0.043*
PEF (L/min)	352.68 $\pm$ 3.881	420.11 $\pm$ 4.77* ^γ	355.17 $\pm$ 3.599	381.09 $\pm$ 3.59*
SpO ₂	93.0 $\pm$ 2.6	96.7 $\pm$ 2.9* ^γ	93.4 $\pm$ 2.3	94.4 $\pm$ 2.5*

FVC: forced vital capacity, FEV₁: forced expiratory volume in one second, PEF: peak expiratory flow, SpO₂: pulse oximetry. Data are expressed as means $\pm$ SEM

(standard error of the mean). n = Number of patients. Baseline values were not significantly different between the two groups ($p > 0.05$). Endpoint values were

significantly different from baseline values ($p < 0.05$) in both groups.

⁷ Endpoint values of bambuterol group are significantly different from endpoint values of zafirlukast group ($p < 0.05$).

4. DISCUSSION

The main aims of asthma management are to control symptoms, maintain pulmonary function close to a normal level and maintain normal physical activity levels.^[12-13] Our study revealed that, after 4 weeks of treatment, bambuterol or zafirlukast were effective in improving and declining the frequency of asthma symptoms and PFT variables among patients with moderate persistent asthma.

Bambuterol hydrochloride is the first once daily oral β_2 -agonist with 24 h duration for the treatment of asthma. It is a prodrug of terbutaline, with a considerable presystemic and metabolic stability, designed to be slowly metabolized to terbutaline.^[14-15] The pharmacologic effects of bambuterol are at least in part attributable to stimulation through β_2 -adrenergic receptors of intracellular adenylate cyclase, the enzyme that catalyzes the conversion of ATP to cyclic AMP. Increased cyclic AMP levels are associated with relaxation of bronchial smooth muscle and inhibition of mediator release from primed mast cells.^[16-17] It has similar clinical efficacy to other oral bronchodilators, but with less side-effects, especially with regard to tremor.^[18] The low occurrence of side-effects may be due to the smooth and sustained plasma levels of terbutaline generated at steady-state.^[19] The long half-life of bambuterol (20 hours) allows once-daily dosing. Bambuterol 20 mg improved nocturnal asthma symptoms and reduced the overnight dip in peak flow rate more effectively than did placebo in patients who had remained symptomatic despite treatment with inhaled or oral corticosteroid.^[20] In contrast Persson et al., (1995), showed that treatment with 10 mg bambuterol did not show a statistically significant difference versus placebo as measured by FEV₁, 24 hours after administration.

Asthma considered a bronchoconstrictive disease of airway smooth muscle and is recently regarded as a chronic inflammatory disorder of the airway.^[21] Even in mild to-moderate asthma, a strong inflammatory process is present which is believed to be the underlying cause of airway hyper-responsiveness and propensity to airway obstruction.^[22] Zafirlukast has been shown to reduce bronchoconstriction induced by several stimuli, including LTD₄, allergens, exercise, and cold air, sulphur oxide or platelet activating factor.^[23-24] Significantly increased the morning PEF and FEV₁, and decreased daytime asthma symptoms, night-time awakenings, mornings with asthma and β_2 -agonist use occurred in patients received zafirlukast. Its effects appeared within two days.^[25] It is known from clinical

studies that the pharmacodynamics of zafirlukast show dose response to a certain degree, but e.g. twofold increase in the dose (from 20 mg to 40 mg twice daily or from 40 to 80 mg twice daily) does not affect the asthma symptoms or decrease the need for β_2 -agonist use.^[26] In vivo studies showed that the releases of CysLTs in asthmatic patients are recovered in the airways in concentrations matching asthma severity score.^[3] Moreover, they have been shown to play an important role in the pathogenesis of asthma.^[27] Zafirlukast is one of the leukotrienes modifiers which inhibiting a specific pathway or mediator in the vast array of inflammatory pathways that have established efficacy in asthma.^[28]

Leukotrienes modifiers are considered as anti-inflammatory and they are associated with a decreased level of exhaled nitric oxide, (a marker of air way inflammation) and decreased serum eosinophils.^[29-30] Zafirlukast was recently found to block CysLTs-mediated activation of human helper T cell that release proinflammatory cytokines in asthmatic airways.^[31] It has been found that zafirlukast inhibits the production of TGF β 1,2 which is believed to play a significant role in bronchial remodeling.^[32]

In conclusion, both zafirlukast and bambuterol were effective in improving pulmonary function and asthma-related symptoms in patients with moderate persistent asthma however, bambuterol showed more significant improvement in PFT values compared to zafirlukast.

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