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Bambuterol versus Montelukast in Patients with Chronic Asthma.

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Research Article

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ABSTRACT

Asthma is a common chronic inflammatory disorder of the airways. This feature of asthma has implications for the diagnosis, management, and potential prevention of the disease. Although many drug classes are used for long-term control of asthma, the response is variable due to multifactorial reasons. This study was designed to evaluate the preventive effect of bambuterol or montelukast sodium in chronic asthmatics. Open-label clinical trial was utilized, in which 40 patients with moderate persistent asthma were randomized into two groups; the first group comprises 20 patients, treated with bambuterol (20 mg orally once daily) for 4 weeks and the second group comprises 20 patients, treated with montelukast sodium (10mg orally once daily) for 4 weeks. Frequency of asthma symptoms (chest tightness, coughing and wheezing), pulmonary function tests (PFTs) and pulse oximetry (SpO_2) were recorded at baseline and at the end point (after 4 weeks). The patients' use of asthma drugs and their symptoms were evaluated at each visit. Results showed that the symptoms of asthma, PFT values and SpO_2 were significantly improved in the two groups at the end of the study compared to the first visit ($p < 0.05$). In conclusion, both bambuterol and montelukast sodium showed significant improvement in asthma symptoms, pulmonary function test values and pulse oximetry after 4-week therapy, however, bambuterol showed more significant improvement in PFT values compared to montelukast.

INTRODUCTION

Asthma is a common chronic disorder of the airways that involves a complex interaction of airflow obstruction, bronchial hyperresponsiveness and inflammation. This interaction can be highly variable among patients and within patients over time [1]. Acute and chronic inflammation can affect not only the airway caliber and airflow but also underlying bronchial hyperresponsiveness, which enhances susceptibility to bronchospasm [2]. 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 [3]. 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 [4]. They induce bronchoconstriction, mucous secretion, increased vascular permeability, and by this way they play an important role in the pathophysiology of asthma [5,6,7]. Antileukotriene agents, including montelukast, zafirlukast, pranlukast and the 5-lipoxygenase inhibitor zileuton, act by blocking the effects of the cysteinyl leukotrienes [8,9]. Montelukast sodium is a potent oral leukotriene-D4-receptor antagonist (cysteinyl leukotriene [Cys LT 1]-receptor antagonist) approved for the treatment of chronic asthma in patients aged 6 years and older [10,11]. Bambuterol is a long acting β- adrenoceptor agonist (LABA) used in the treatment of asthma. It is a biscarbamate ester prodrug of the β_2-adrenoceptor agonist terbutaline Bambuterol, which is inactive at adrenergic receptors, is converted to terbutaline via oxidation and hydrolysis primarily by butyrylcholinesterase [12,13]. 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 designed to evaluate the preventive effect of bambuterol or montelukast sodium in patients with moderate persistent asthma.

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PATIENTS AND METHODS

Forty patients with moderate persistent asthma were recruited from the Outpatient Clinic at Al-Amal Specialized Hospital and divided randomly into two groups 20 patient each. The 1st group: 20 patients, 18 males and 2 females aged 42 ± 11 years, were given bambuterol (Bambec, AstraZeneca) 20 mg orally once daily. The 2nd group: 20 patients, 15 males and 5 females aged 40 ± 11 years were given montelukast (Singulair, MSD) 10mg orally once 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 (wheeze, cough, chest tightness) (3) Nocturnal symptoms > 1/week (4) Forced expiratory volume in one second (FEV1) or peak expiratory flow (PEF) 60-80% predicted values, (5) No history or symptoms of cardiovascular disease, (6) No use of oral or parenteral corticosteroids within 6 weeks, (7) No pregnancy and (8) No use of tobacco products within the previous year.

During the study, patients continued to take a short-acting inhaled β_2-agonist as necessary to relive symptoms. The study protocol was approved by the Research Ethics Committee of Al-Amal 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 SpO_2 was measured with a Palco Oximeter model 30 (Palco Laboratories, Inc., Santa Cruz, CA, USA).

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 statistic analysis was carried out by using SSPS 15.0. The level of significance was set $p < 0.05$.

RESULTS

Asthma symptoms

As demonstrated in Table 1, the mean monthly frequency of asthma symptoms was not significantly different between the 1st (bambuterol) and the 2nd (montelukast) groups at the start of the study ($p > 0.05$). The frequency of all asthma symptoms was significantly reduced in both groups after 1 month of treatment $p < 0.05$). At the study endpoint, the mean monthly frequency of asthma symptoms was significantly reduced in bambuterol group compared to montelukast group ($p < 0.05$).

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

Asthma Symptoms	Bambuterol (n = 20)		Montelukast (n = 20)	
	Baseline (Pre-treatment)	Endpoint (Post-treatment)	Baseline (Pre-treatment)	Endpoint (Post-treatment)
Coughing	6.24 ± 1.90	2.35 ± 0.57*	6.68 ± 1.07*	3.08 ± 0.98*
Night wheeze	9.14 ± 1.82	2.16 ± 0.78*	9.92 ± 2.1*	2.72 ± 0.82*
Daytime wheeze	10.88 ± 2.58	6.72 ± 1.37*	11.12 ± 2.85*	7.22 ± 1.66*

*Post-treatment values were significantly different from pre-treatment (baseline) values ($p < 0.05$) in both groups. Data are expressed as means ± 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 montelukast and bambuterol patient groups compared to first visit ($p < 0.05$). The improvement in PFT values was more significant with bambuterol compared with montelukast.

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

Pulmonary Function Tests and Pulse Oximetry	Bambuterol (n = 20)		Montelukast (n = 20)	
	Baseline (Pre-treatment)	Endpoint (Post-treatment)	Baseline (Pre-treatment)	Endpoint (Post-treatment)
FVC (L)	2.78 ± 0.056	3.72 ± 0.091*α	2.91 ± 0.079	3.16 ± 0.068*
FEV_1 (L)	2.42 ± 0.058	3.28 ± 0.083*α	2.52 ± 0.071	2.77 ± 0.056*
PEF (L/min)	350.73 ± 3.946	415.43 ± 4.67*α	356.06 ± 3.485	398.02 ± 3.686*
SpO_2	93.6 ± 2.9	96.4 ± 2.7*α	93.2 ± 2.4	95.0 ± 2.7*

FVC: forced vital capacity, FEV_1: forced expiratory volume in one second, PEF: peak expiratory flow, SpO_2: pulse oximetry. Data are expressed as means ± SEM (standard error of the mean). n = Number of patients. Pre-treatment values were not significantly different between the two groups ($p > 0.05$). *Post-treatment values were significantly different from pre-treatment (baseline) values ($p < 0.05$) in both groups. αSignificantly different from montelukast group ($p < 0.05$).

DISCUSSION

The results of this study indicate that, after 4 weeks of treatment, montelukast sodium and bambuterol were effective in improving asthma symptoms and PFT variables among patients with moderate persistent asthma. The frequency of asthma symptoms declined in both treatment groups; some patients were almost symptom free at the end of the study. The main aims of asthma management are to control symptoms, maintain pulmonary function close to a normal level and maintain normal physical activity levels [14,15]. After many years of being considered a bronchoconstrictive disease of airway smooth muscle, asthma is recently regarded as a chronic inflammatory disorder of the airway [16]. Even in mild to-moderate asthma, a strong inflammatory process is present. This inflammation is believed to be the underlying cause of airway hyper-responsiveness and propensity to airway obstruction [17]. In recent studies in adults, montelukast sodium (10 mg) administered once daily at bed time demonstrated improvement in variables of asthma control, including forced expiratory volume in one second (FEV1) day time and night-time symptoms, and as-needed β-agonist use [18,19]. At the level of childhood asthma, montelukast reduces asthma exacerbations in children with intermittent asthma [20]. In vivo studies showed that the release of CysLTs in asthmatic patients are recovered in the airways in concentrations matching asthma severity score. [4]Moreover, they have been shown to play an important role in the pathogenesis of asthma [21]. Montelukast is one of the leukotrienes modifiers which are the first drugs inhibiting a specific pathway or mediator in the vast array of inflammatory pathways that have established efficacy in asthma [22]. 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 [24,25]. Montelukast was recently found to block CysLTs-mediated activation of human helper T cell that release proinflammatory cytokines in asthmatic airways [25]. It has been found that montelukast inhibits the production of TGF-β1 which is believed to play a significant role in bronchial remodeling [26]. Also, results of the present study showed significant improvements in asthma symptoms and PFTs with bambuterol therapy compared to baseline findings. 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 [27,28]. 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 [29,30]. It has similar clinical efficacy to other oral bronchodilators, but with less side-effects, especially with regard to tremor [31]. The low occurrence of side-effects may be due to the smooth and sustained plasma levels of terbutaline generated at steady-state [32]. 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 [33]. According to Persson et al., treatment with 10 mg bambuterol did not show a statistically significant difference versus placebo as measured by FEV1, 24 hour after administration. However, the 24 hour effect duration of 20 mg bambuterol was confirmed by the improvements demonstrated in FEV1 after 1 and 4 weeks treatment, as compared with placebo. In conclusion, both montelukast 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 montelukast.

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