Bambuterol versus Montelukast in Patients with Chronic Asthma

Ahmed M. Ali
Department of Clinical Pharmacy
Faculty of Pharmacy, October 6 University
October 6 City, Central Axis, Part 1/1, Giza Governate, Egypt
Email: ahmedzogary [AT] yahoo.com

ABSTRACT---- ***Background: 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.***

Subjects and methods: 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 (10 mg 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: 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.

Keywords- Bambuterol; Montelukast sodium; Moderate persistent asthma; Pulmnory function tests.

1. 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.

2. SUBJECTS 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) 10 mg 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 $p < 0.05$.

3. 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.

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*$^{\alpha}$	2.91 ± 0.079	3.16 ± 0.068*
FEV_1 (L)	2.42 ± 0.058	3.28 ± 0.083*$^{\alpha}$	2.52 ± 0.071	2.77 ± 0.056*
PEF (L/min)	350.73 ± 3.946	415.43 ± 4.67*$^{\alpha}$	356.06 ± 3.485	398.02 ± 3.686*
SpO_2	93.6 ± 2.9	96.4 ± 2.7*$^{\alpha}$	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. $^{\alpha}$Significantly different from montelukast group ($p < 0.05$).

4. 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 releases 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 [23-24].

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 β2-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 β2-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., (1995), 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.

5. REFERENCES

1. Busse WW, Lemanske RF Jr. Asthma. N Engl J Med. 2001; 344(5):350–62.

2. Cohn L, Elias JA, Chupp GL. Asthma: mechanisms of disease persistence and progression. Annu Rev Immunol. 2004; 22:789–815.

3. Maddox L, Schwartz DA. The pathophysiology of asthma. Annu. Rev. Med. 2002; 53: 477-498.

4. Hay DW, Trophy TJ, Undem BJ. Cysteinyl leukotrienes in asthma: old mediators up to new tricks. Trends Pharmacol. Sci. 1995; 16(9):304-309.

5. Shield MD., Brown V, Stevenson EG., Fitch PS., Schock BC et al. Serum eosinophilic cationic protein and blood eosinophil counts for the prediction of the presence of airways inflammation in children with wheezing. Clin. Exp. Allergy1999; 29: 1382-1389.

6. Strauch E., Moske O, Thomas S, Storm Van's Gravesande K, Ihorst, G et al. A randomized controlled trial on the effect of montelukast on sputum eosinophil cationic protein in children with corticosteroid-dependent asthma. Pediatr. Res. 2003. 54: 198-203.

7. Mechiche H. Naline E, Candenas L, Pinto, P.M., Birembault P et al. Effects of cysteinyl leukotrienes in small human bronchus and antagonist activity of montelukast and its metabolites. Clin. Exp. Allergy 2003; 33: 887-894.

8. Reiss TF, Sorkness CA, Stricker W, Botto A, Busse WW et al. Effects of montelukast (MK-0476); a potent cysteinyl leukotriene receptor antagonist, on bronchodilation in asthmatic subjects treated with and without inhaled corticosteroids. Thorax 1997a; 52: 45-48.

9. Villaran C, O'Neill SJ, Helbling A. Montelukast versus salmeterol in patients with asthma and exercise-induced bronchoconstriction. Montelukust/Salmeterol Exercise Study Group. J. Allergy Clin. Immunol. 1999; 104: 547-553.

10. Reiss TF, Chervinsky P, Dockhorn RJ, Shingo S, Seidenberg B et al. Montelukast, a once daily leukotriene receptor antagonist in the treatment of chronic asthma: a multi-center randomized, double-blind trial. Arch. Intern. Med. 1998; 158:1213-1220.

11. Krawiec ME, Jarjour NJ. Leukotriene receptor antagonists. Semin. Respir. Crit.Care Med. 2002; 23: 399-410.

12. Sitar DS. Clinical pharmacokinetics of bambuterol. Clin Pharmacokinet. 1996; 31:246-56.

13. Rosenborg J, Larsson P, Nyberg L. Pharmacokinetics of bambuterol during oral administration of plain tablets and solution to healthy adults. Br J Clin Pharmacol 2000; 49:199-206.

14. Global Initiative for Asthma (GINA). Global strategy for asthma management and prevention: NHLBI/WHO Workshop Report: Bethesda: National Institutes of Health, National Heart, Lung and Blood Institute; 2002. Publication No. 02-3659.

15. Boskabady MH, Fasihfar M. Correlation between symptom score, reversibility of pulmonary function tests and treatment response in asthma. Iran. J. Allergy Asthma Immunol. 2003; 2 (2): 61-67.

16. Holgate ST. The cellular and mediator basis of asthma in relation to natural history. Lancet 1997; 350 (Suppl. 2): SII5-SII9.

17. Pavord ID, Ward R, Woltmann G, Wardlaw AI, Sheller JR et al. Leukotriene C4 induces TGF-beta1 production in airway epithelium via p38 kinase pathway. Am J Respir Cell Mol Biol. 2006; 34:101-7.

18. Reiss TF, White R, Noonan G, Korenblat P, Hess J et al. Montelukast (MK-0467), a CysLT 1 receptor antagonist improves the signs and symptoms of asthma over one year of treatment. Eur. Respir. J. 1997b; 10 (Suppl. 25): 437S-438S.

19. Reiss TF, Chervinsky P, Edwards T. Montelukast (MK-0467), a CysLT 1 receptor antagonist, improves asthma outcomes over a 3-month treatment period. Am. J. Respir. Crit. Care Med. 1997c; 155: A662.

20- Bisgaard H, Zielen S, Garcia-Garcia ML, Johnston SL, Gilles L, Menten J, Tozzi AC, Polos P, et al. Montelukast reduces asthma exacerbations in 2. to 5-year-old children with intermittent asthma. Am. J. Respir. Crit. Care Med. 2005; 171 (4): 315-322.

21. Barnes PJ, Chung KF, Page C. Inflammatory mediators of asthma: an update. Pharmacol. Rev. 1998; 50: 515-596.

22. Keam SJ, Lyseng-Williamson KA, Goa KL. Pranlukast: a review of its use in the management of asthma. Drugs 2003; 63:

991-1019.

23. Fritscher LG, Rodrigues MT, Zamel N, Chapman KR. The effect of montelukast on exhaled nitric oxide of alveolar and bronchial origin in inhaled corticosteroid-treated asthma. Respir Med. 2009; 103(2):296-300.

24. Schäper C, Noga O, Koch B, Ewert R, Felix SB et al. Anti-inflammatory properties of montelukast, leukotriene receptor antagonist in patients with asthma and nasal polyposis. J Investig Allergol Clin Immunol. 2011; 21(1):51-58.

25. Xue L, Barrow A, Fleming VM, Hunter MG, Ogg G et al. Leukotriene E_4 activates human Th_2 cells for exaggerated proinflammatory cytokine production in response to prostaglandin D_2. J. Immunol. 2012; 188(2):694-702.

26. Majak P, Rychlik B, Pu1aski L, B1auz A, Agnieszka B et al. Montelukast treatment may alter the early efficacy of immunotherapy in children with asthma. J Allergy Clin Immunol. 2010; 125(6):1220-1227.

27. Svensson LA. Bambuterol, a bronchodilator prodrug with sustained action, enhances delivery of active drug to the lung. Agents Actions Suppl. 1988; 23:271-276.

28. Waldeck B. Beta-adrenoceptor agonists and asthma-100 years of development. Eur J Pharmacol. 2002; 445:1-12.

29. Svensson LA. Mechanism of action of bambuterol: a beta-agonist prodrug with sustained lung affinity. Agents Actions Suppl. 1991; 34:71-78.

30- Chou YL, Wu CC, Wang HW. Effects of bambuterol and terbutaline on isolated rat's tracheal smooth muscle. Eur Arch Otorhinolaryngol. 2010; 267(8):1305-11.

31. Larsen K, Schmekel B. Tremor in healthy volunteers after bambuterol and terbutaline CR-tablets. Eur J Clin Pharmacol. 1993; 45: 303–305.

32. Persson G, Baas A, Knight A, Larsen B, Olsson H. One month treatment with the once daily oral β2-agonist bambuterol in asthmatic patients. Eur Respir J. 1995; 8: 34–39.

33. Petrie GR, Chookang JY, Hassan WU, et al. Bambuterol: effective in nocturnal asthma. Respir Med. 1993; 87:581-5.