Comparative clinical evaluation of ketotifen and montelukast sodium in asthmatic Iraqi patients

Fadyia Y. Al-Hamdani *

College of Pharmacy, University of Baghdad, Clinical Pharmacy Department, Iraq

Received 10 April 2010; accepted 10 July 2010
Available online 29 July 2010

KEYWORDS
Ketotifen; Montelukast sodium; Asthma symptom score; Pulmonary function test

Abstract  Asthma is a common and chronic inflammatory condition of the airways whose cause is not completely understood. Although many classes of drugs are used for management of asthma, the response is variable due to multifactor reasons. This study was designed to evaluate the outcome of using ketotifen or montelukast sodium in Iraqi asthmatic patients. Single blinded randomized clinical trial was utilized, in which 100 asthmatic patients were recruited from Al-Karama hospital and randomized into two groups; 1st group (50 patients, treated with ketotifen for 4 weeks) and 2nd group (50 patients treated with montelukast sodium for 4 weeks). Asthma symptom score and wheezing were recorded at the beginning (first visit) and at the end of the study (after one month). Pulmonary function tests (PFTs) were performed by spirometry, and the patients’ use of asthma drugs and their symptoms were evaluated at each visit. The result showed that asthma symptom, chest wheezing, and PFT values were significantly improved in the two groups at the end of the study compared to first visit ($p < 0.05$). All symptoms were significantly lower and PFT values were higher in the 2nd group compared to 1st group ($p < 0.05$). In conclusion, both ketotifen and montelukast sodium showed significant changes in asthma symptoms and PFT after one month of treatment, but the changes were more significant with montelukast group (2nd group) compared with ketotifen group (1st group) and this indicate that montelukast was more effective than ketotifen in treatment of asthmatic patients.

1. Introduction

Although the occurrence of asthma has increased significantly over the last decades in children and adults (Gibson et al., 1998), 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 (Maddox and Schwartz, 2002). Cysteinyl leukotrienes, 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 (Hay et al., 1995). They induce bronchoconstriction, mucous secretion, increased vascular permeability (Shield et al., 1999; Strauch et al., 2003), and by this way they play an important role in the pathophysiology of asthma (Mechiche et al., 2003). Antileukotriene agents, including montelukast, zafirlukast, pranlukast and the 5-lipoxygenase inhibitor zileuton, act by blocking the effects of the cysteinyl leukotrienes (Reiss et al., 1997a; Villaran et al., 1999). Montelukast sodium (singulair) is a potent, oral-specific leukotriene D4-receptor antagonist (cysteinyl leukotriene [Cys LT 1]-receptor antagonist) recently approved for the treatment of chronic asthma in patients aged 6 years and older (Reiss et al., 1998; Krawiec and Jarjour, 2002); on the other hand, the first-generation H1-antihistamine ketotifen and the second-generation H1-antihistamine cetirizine, both have anti-allergic and anti-inflammatory properties and have been used with some success in the secondary prevention of asthma (Dyson and Mackay, 1980; Bisgaard et al., 2005). Ketotifen, an orally active tricyclic benzocycloheptathiophene derivative, has several properties suggesting that it might be useful in the management of asthma. (Bustos et al., 1995) It inhibits passive cutaneous anaphylaxis and has a mast cell stabilizing effect. It is also a potent antihistamine specific for H1 receptors with little anticholinergic activity and it raises intracellular cyclic-AMP levels by inhibiting phosphodiesterase (Grant et al., 1992). It may also interfere with the lipoxygenase pathway of arachidonic acid metabolism (Lane, 1980). The present study was designed to evaluate the clinical efficacy of ketotifen and montelukast sodium in treatment of Iraqi asthmatic patients.

2. Patients and methods

One hundred patients with moderate asthma, were recruited from the Asthma Clinic in Al-Karama Medical Centre and divided randomly into two groups (1st group: 50 patients, 15 female, aged 45 ± 11 years), were given 1 mg ketotifen (Zaditen, Novartis) orally and (2nd group: 50 patients, 16 female, aged 40 ± 11 years) were given 10 mg montelukast (Singulair, MSD) orally.

Inclusion criteria were: (1) Previously diagnosed asthma. (2) Presence of two or more of the following symptoms: recurrent wheeze, cough or chest-tightness at rest, nocturnal or early morning wheeze, cough or chest-tightness and wheeze or cough during exercise. (3) Forced Expiratory Volume at one second FEV1 and Peak Expiratory Flow PEF less than 80% predicted values. (4) No history or symptoms of cardiovascular, life threatening or uncontrolled asthma. (5) No use of oral or parental corticosteroids within 6 weeks. (6) No pregnancy and no use of tobacco products within the previous year. During the study, patients continued to take a short-acting inhaled β2-agonist as necessary to control symptoms. All patients signed written informed consent to participate in the study.

The study was performed in single blind manner. Medical examination was performed and asthma symptoms were taken at the beginning and the end of the study for each patient. Asthma symptom score was counted according to Clinical Asthma Score (CAS); a modification of the Woods Downes asthma score, to objectively evaluate our asthmatic patients’ degree of respiratory distress. This score evaluates three aspects of a patient’s respiratory distress: (1) degree of wheezing, (2) degree of retraction and/or flaring (3) degree of dyspnea. Each category is given a score of 0–3, so the total score ranges from 0 to 9, with 9 being the worst score.

The degree of wheezing was considered between 0 and 3 as follows: no wheezing = 0, hardly heard wheezing = 1, moderate wheezing = 2 and loud wheezing = 3.

Pulmonary function test was also measured in the beginning and at the end of the study using a pneumotachograph sensor (Model ST 90, Fukuda, Sangyo Co., Ltd., Japan). Pulmonary function testing was performed using the acceptability standards outlined by the American Thoracic Society (ATS) with subjects in a standing position and wearing nose clips (ATS, 1994). All tests were carried out between 1000 and 1700 h. Pulmonary function test was performed three times from each subject. The highest level for forced vital capacity (FVC), (FEV1), peak expiratory flow rate (PEFR), vital capacity (VC) were taken independently from the three curves. The criteria for asthma severity score were included in Table 1.

The degree of wheezing was considered between 0 and 3 as follows: no wheezing = 0, hardly heard wheezing = 1, moderate wheezing = 2 and loud wheezing = 3.

2.1. Experimental design and analysis of data

The study design was Rationalized Complete Block Design (RCBD). 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 at *, ** which represent P < 0.05 and P < 0.001, respectively.

3. Results

3.1. Asthma symptoms

All symptom scores of asthmatic patients treated according to Clinical Asthma Score (CAS) were improved in the 2nd group after 1 month’s treatment, (P < 0.001) for all cases, and were significantly reduced in the 2nd group in comparison to the 1st group subjects at the end of the study (P < 0.001) (Table 2). However, in the 1st group there was a small improvement in some symptoms between the first and last visits only (P < 0.01 for all cases). Asthma symptoms were not different between the 1st and 2nd groups at the start of the study. Asthma severity score and chest wheezing were also improved at the end in the 2nd group (P < 0.001 for each measure). While

<table>
<thead>
<tr>
<th>Table 1 The criteria for asthma severity score.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptom</td>
</tr>
<tr>
<td>Night wheezing</td>
</tr>
<tr>
<td>Sleeping well with a little wheezing</td>
</tr>
<tr>
<td>Waking once at night</td>
</tr>
<tr>
<td>Waking most of night</td>
</tr>
</tbody>
</table>

The degree of wheezing was considered between 0 and 3 as follows: no wheezing = 0, hardly heard wheezing = 1, moderate wheezing = 2 and loud wheezing = 3.
at the beginning of the study, there was no significant difference in asthma severity score and chest wheezing between the 1st and 2nd groups, at the end of the study all parameters in the 2nd group became significantly lower than the 1st group \((P < 0.001\) for all cases), (Table 2).

### 3.2. Pulmonary function tests

Pulmonary function test (PFT) values were significantly improved in the two groups after 4 weeks compared to first visit \((P < 0.05\) for all measures). The improvement occurred primarily within 1 month. While there was no significant difference in PFT variables between 1st and 2nd groups \((P < 0.8)\) at the beginning of the study, however, the improvement was more significant with montelukast sodium comparing with ketotifen, Table 3.

### 4. Discussion

The results of this study indicate that, after four weeks of single-blind treatment, montelukast sodium was more effective than ketotifen in improving asthma symptoms and pulmonary function among asthmatic patients. Treatment with montelukast sodium. Resulted in significantly greater improvements in PFT values after only a short period of treatment. The asthma symptom scores also improved more in the 2nd group; these patients were almost symptom free at the end of the study. In recent studies in adults, montelukast sodium (10 mg) administered once daily at bed time demonstrated improvement in variable of asthma control, including forced expiratory volume in one second (FEV1) day time and nighttime symptom scores, and as-needed B-agonist use (Reiss et al., 1997b,c, 1995; National Institutes of Health, 2002). The main aims of asthma management are to control symptoms, maintain pulmonary function close to a normal level and maintain normal physical activity levels (Boskabady and Fasihfar, 2003; National Heart, Lung, and Blood Institute, 2002).

After many years of being considered a bronchoconstrictive disease of airway smooth muscle, asthma is now regarded as a chronic inflammatory disorder of the airway (Holgate, 1997). Even in mild to-moderate asthma, a strong inflammatory process is present. This inflammation is believed to be the

#### Table 2  Asthma symptoms and severity in the two groups of patients at the beginning, and the end of the study.

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Pre-treatment</th>
<th>Post-treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1st gr.</td>
<td>2nd gr.</td>
</tr>
<tr>
<td>Night wheezing</td>
<td>2.12 ± 0.90</td>
<td>1.73 ± 0.92</td>
</tr>
<tr>
<td>Night coughing</td>
<td>1.67 ± 1.09</td>
<td>1.81 ± 1.17</td>
</tr>
<tr>
<td>Morning W and C</td>
<td>1.50 ± 1.06</td>
<td>1.42 ± 1.03</td>
</tr>
<tr>
<td>Daily W, C and T</td>
<td>2.04 ± 0.85</td>
<td>1.81 ± 0.85</td>
</tr>
<tr>
<td>Chest wheezing</td>
<td>2.33 ± 0.76</td>
<td>2.19 ± 0.63</td>
</tr>
<tr>
<td>Asthma severity</td>
<td>2.67 ± 1.01</td>
<td>2.23 ± 0.82</td>
</tr>
</tbody>
</table>

Gr.: group, W: wheezing, C: coughing, T: tightness of chest.

All values were quoted as means ± SEM. Statistical difference in different parameter: non significant difference, **\(P < 0.001\).
Gr.: group, W: wheezing, C: coughing, T: tightness of chest.

#### Table 3  Effects of ketotifen and montelukast on pulmonary function tests.

<table>
<thead>
<tr>
<th></th>
<th>Ketotifen ((n = 50))</th>
<th>Montelukast ((n = 50))</th>
</tr>
</thead>
<tbody>
<tr>
<td>FVC</td>
<td>Pre-treatment</td>
<td>65.06 ± 0.729</td>
</tr>
<tr>
<td></td>
<td>Post-treatment</td>
<td>75.28 ± 0.723(^a)</td>
</tr>
<tr>
<td>PEFVR</td>
<td>Pre-treatment</td>
<td>351.73 ± 3.946</td>
</tr>
<tr>
<td></td>
<td>Post-treatment</td>
<td>397.02 ± 3.686(^a)</td>
</tr>
<tr>
<td>FEV</td>
<td>Pre-treatment</td>
<td>2.41 ± 0.058</td>
</tr>
<tr>
<td></td>
<td>Post-treatment</td>
<td>2.79 ± 0.073(^a)</td>
</tr>
<tr>
<td>VC</td>
<td>Pre-treatment</td>
<td>2.79 ± 0.056</td>
</tr>
<tr>
<td></td>
<td>Post-treatment</td>
<td>3.15 ± 0.068(^a)</td>
</tr>
</tbody>
</table>


Data are expressed as means ± SEM.

\(n\) = Number of patients.

\(^{a}\) \(P < 0.05\) with respect to baseline value.

Pre-treatment values were not significantly different between the two groups \((P > 0.05)\).

Non-identical superscripts (a, b) represents significant difference between the two groups \((P < 0.05)\).
underlying cause of airway hyper-responsiveness and propensity to airway obstruction (Pavord et al., 1999). In vivo studies showed that the release of cysteinyl leukotrienes in asthmatic patients are recovered in the airways in concentrations that parallel asthma severity score (Hay et al., 1995). Moreover, they have been shown to play an important role in the pathogenesis of asthma (Barnes et al., 1998).

Montelukast is one of the leukotrienes modifiers (LT 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 (Keam et al., 2003). These LT modifiers are often considered as anti-inflammatory and they are associated with: (i) a decrease in fraction of exhaled nitric oxide (FeNO) that is considered a marker of airway inflammation; (ii) reduced serum eosinophils; and (iii) decreased sputum eosinophils (Rackham et al., 1989).

At the same time there was significant improvement in PFT observed with ketotifen comparing to the first reading and this was related to the fact that anti-histamines such as ketotifen, cetirizine and loratidine have shown a range of effects upon asthma (Kabra et al., 2000; Makino, 1966), since histamine is one of the inflammatory mediator within the respiratory tract which acts as a bronchoconstrictor in patients with asthma (Martin and Romer, 1977; Coyle et al., 1996), beside that ketotifen a slow onset anti-histamine, reduced the IL-5 (one of Type 2 T helper cell-derived cytokines which are critical in the development and progression of allergic air way diseases. Induced increase in the eosinophil, neutrophil, and epithelial cell populations and pulmonary inflammation, especially the desquamation of bronchial epithelial cells (Iwama et al., 1992).

Also it may slowly modulate the Th2-related chemokine production for later improvement of asthma, while montelukast compete with the late-asthma mediator and cause a faster symptom release (Hung et al., 2005).

In conclusion montelukast is found more effective than ketotifen in improving pulmonary measures and asthma-related symptoms in Iraqi asthmatic patients.

References


