Role of of Montilukaste with or without Desloratidin in treatment of Bronchial Asthma

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Received 14/2/2012 Accepted 20/5/2012

Abstract

The role of leukotriens antagonist alone and with the new generation H1 antihistaminics is not well elucidated. This study has been designed to evaluate the role of montilukast with and without desloratidine in the treatment of mild to moderate severity bronchial asthma. This is a double blind placebo control clinical trial which has been conducted on 150 patients with mild to moderate bronchial asthma in the period between July 2011 to January 2012 in Tikrit General Hospital and Private Clinic. The patients were divided into 3 groups, first group received montilukast alone, the second group received montilukast plus desloratidine and the third group received placebo tablet. Forced expiratory volume in first second (FEV1), Peak expiratory flow rate (PEFR), and Asthmatic Symptom Score were measured before and after the treatment period of three months. There was a significant improvements in all parameters in the montilukast group ($P \leq 0.01$). The combination of montilukast with desloratidIne resulted in a highly significant improvement in all parameters ($P \leq 0.001$). From this study we conclude that montilukast is a useful drug in the armamentarium against asthma, however the addition of desloratidine appears to have synergistic action in patients with mild to moderate bronchial asthma

Key words: Bronchial Asthma Treatment, Montilukast, Desloraidine.

دراسة دور المونتيلوكاست مع أو بدون الدسلوراتدين في علاج مرضى الربو التشعبي

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الخلاصة

ان دور مضادات الليوكوترين مع او بدون الاجيال الحديثة من مضادات الهستامين فى علاج مرضى الربو لم تتم دراستها بصورة واضحة . اجريت هذه الدراسة المسيطر عليها بالبلاسيبو على 150 مريضا مصابين بالربو الشعبي الخفيف والمعتدل الشدة ، وقد قسم المرضى الى ثلاثة مجاميع كل مجموعة من 50 مريض المجموعة الاولى عولجت بالمونتلوكاست وال مجموعة الثانية عولجت بالمونتلوكاست مع الديسلوراتدين ، اما المجموعة الثالثة فقد تم معالجتها بالبلاسيبو . تم اعتماد قياسات كمية الزفير في اول ثانية واعلى نسبة جريان زفيري وكذلك مقياس اعراض الربو لتقييم النتائج . كانت هناك نتائج ذو قيمة احصائية ولكل المقاييس لم جموعة المونتلوكاست($P \leq 0.01$)، بينما كان هناك نتائج ذات قيمة احصائية عالية($p \leq 0.001$). يستنتج من هده الدراسة ان مضادات الليوكوترين مفيدة في علاج الربو الشعبي وان اضافة مضادات الهستامين من الاجيال الجديدة له فائدة اضافية.

Introduction

Asthma is a chronic inflammatory disorder which involve the bronchial tree causing bronchoconstriction and excessive mucous production and infiltration with inflammatory cells causing reversible narrowing of the bronchial tree.[1,2]. Leukotriens are naturally produced eicosanoid lipid mediators which are responsible for the effect of inflammatory response.[3] These potent inflammatory mediators promote neutrophil- endothelial interactions inducing bronchoconstriction and airway hyperresponsiveness. They also stimulate smooth muscle hypertrophy, mucus hypersecretion and attract eosiophils into the airway tissues[4]. Cysteinylleukotiens make up the slow reacting substance of anaphylaxis. Montilukast is a leukotrien receptor antagonist that have been used in the treatment of mild to moderate asthma and for patients with moderate to severe asthma who have systemic side effects from high doses of inhaled corticosteroids and patients with poor response to inhaled corticosteroids or those who can not tolerate theophylline or long acting bronchodilators.[5,6] Histamine is an important mast cell- and basophil-derived mediator that has been implicated in the pathogenesis of asthma, resulting in smooth muscle contraction, mucus hypersecretion, and increased vascular permeability leading to mucosal edema.[7]The usefulness of first-generation antihistamines is limited by their side-effect profile, namely sedation and cognitive impairment. Second-generation antihistamines have only a modest effect in attenuating bronchospasm induced by histamine, cold air, exercise, and allergen bronchoprovocation, suggesting that second-generation antihistamines do not have a direct role as a single agent for treating asthma.[8,9]. Antihistamines have been evaluated as potential therapies for asthma for more than 50 years. With first-generation compounds, side effects prevented effective treatment. Second-generation histamine H1 receptor antagonists are recognized as being highly effective treatments for allergic-based disease and are among the most frequently prescribed drugs in the world. The newer antihistamines represent a heterogeneous group of compounds with markedly different chemical structures, a spectrum of antihistaminic properties, adverse effects, half-life, tissue distribution, metabolism and varying degrees of anti-inflammatory effects.[10]Desloratadine is a biologically active metabolite of the second-generation antihistamine loratadine. Desloratadine is a highly selective peripheral H1 receptor antagonist that is significantly more potent than loratadine. Results of in vitro and in vivo studies have suggested that desloratadine has anti-allergic effects that are unrelated to its ability to antagonist the effects of histamine. Desloratadine inhibits the expression of cell adhesion molecules, inhibits the generation and release of inflammatory mediators and cytokines, attenuates eosinophil chemotaxis, adhesion and superoxide generation. Studies in animals indicate that desloratadine does not cross the blood-brain barrier and therefore does not cause sedation and does not impair cognition or psychomotor performance. Desloratadine has an excellent overall safety profile.[11] Antihistamines have recently been shown to have anti-inflammatory properties that are more extensive than simply the blocking of histamine receptors. For example, new evidence suggests that the suppression of cell adhesion molecule expression occurs with these drugs. The anti-

inflammatory and anti-asthmatic effects of antihistamines have been evaluated in patients with both allergic asthma and rhinitis, given the established association between allergic inflammation of the upper and lower airways, with evidence to suggest that antihistamines have clinically relevant anti-asthmatic properties. As well as conferring benefits in asthma symptom control and the measurement of lung function, studies assessing the effect of histamine receptor antagonists on bronchial hyperresponsiveness suggest that there is bronchoprotection during both methacholine and mannitol challenges. Recently, there has also been considerable interest in the effect of combining an antihistamine with a leukotriene receptor antagonist. This combination has an anti-asthmatic effect that is greater than that of either drug given alone and may be comparable to inhaled corticosteroid therapy.[12] Antihistamines should never be used as monotherapy for asthma but there is evidence that these drugs give a measure of protection in histamine-induced bronchoconstriction. Furthermore, it has been demonstrated that the use of second or third -generation antihistamines, as adjunct therapy may benefit those patients whose asthma is associated with allergic rhinitis.[13]. This study has been designed to evaluate the role of montilukast and montilukast plus deslratidine on parameters of pulmonary function tests (FEV1, PEFR) and Asthmatic symptom scores in Iraqi mild to moderate severity asthmatic patients.

Subjects and Methods

This study is a randomized double blind , placebo controlled, clinical trial . A total of 150 patients with age and gender matched and with mild to moderate asthma were included in this study. It was performed in Tikrit General Hospital and Private Clinic during the period between July2011 to January 2012. The diagnosis of asthma is made according to clinical history and improvement of FEV1≥ 15% 20 minutes after short acting bronchodilator inhalation. The study was approved by the scientific committee of the Medical College of Tikrit University, and personal consent were obtained from all patients. Exclusion criteria include those patients with Acute Sever Asthma, Chronic Obstructive Pulmonary Diseases, Left Sided Heart Failure and Acute Upper Respiratory Tract Infection. PEFR and FEV1were measured for participants before and after the treatment period. The calculation of these parameters were performed according to age, height and gender. Asthma control scoring system were calculated according to the frequency of diurnal symptoms, nocturnal symptoms, beta agonist uses on demand and rate of limitation of physical activity.[14] First group of 50 patients (27female, 23 male) received 10 mg Montilukast once daily' at bed time for 3 months, second group of 50 patients (26 females & 24 males) received Montilukast 10 mg plus Desloratidine 20 mg once daily at bed time and the third group of 50 patients (43 female & 16 male) received placebo drug once daily at bed time for three months also. Descriptive statistics were used tocalculate the mean ,standard deviations, numbers and frequencies. Paired t- test were used to compare measured parameters before and after treatment. ANOVA test were used to compare the results between the three groups. All statistical results were considered significant at the level of ($p \leq 00.05$).

Results

One hundred and fifty patients has participated in this study .Table 1

shows the characteristics of these patients according to gender and age. The difference between the 3 groups were statistically not significant. Table 2 shows the results of the measured parameters between the three groups (Montilukast, Montilukast plus desloratidine and Placebo) before treatment. There was no statistically differences of the three parameters used in this study between the three groups of patients. The differences in the respond to treatment by Montilukast versus placebo is shown in table 3, there is a statistically significant differences at the level of ($p \leq 0.01$). Table 4 illustrate the differences in response to the three parameters between Montilukast plus desloratidine and placebo. The results shows that there is highly statistically significant differences of the three parameters between the two groups at the level of ($p \leq 0.001$). The differences in the response of the measured parameters between Montilukat and Montilukast plus Montilukast plus desloraidine is shown in table5. There is a highly statistically significant differences at the level of ($p \leq 0.001$) between all the measured groups.

Table (1):- Subject Characteristics

Characteristic	montilukast	Montilukast+desloratidine	placebo	P Value
No	50	50	50	Not Significant
Gender	Male : 43.5% Female : 56.5%	Male : 39% Female : 61%	Male : 47.6% Female52.4%	=
Age (Mean)	33	34.5	33.2	=

Table (2):- FEV1, PEFR and Symptoms score of Groups Before Treatment

Parameter	Montilukast	Montilukast+ desloratidine	Placebo	P value
FEV1	2.52 ± 0.24	2.50 ± 0.23	2.50 ± 0.24	Not Significant
PEFR	305.22 ± 19.94	320 ± 30.63	315.5 ± 17.61	Not Significant
Symptoms Score	64.1 ± 5.71	63.3 ± 5.82	63.3 ± 5.82	Not Significant

Table (3):- FVC1 FEV1 and Symptoms score of Montilukast and Placebo groups after treatment

Parameter	Montilukast	Placebo	P value
FEV1	2.76± 0.23	2.39± 0.22	0.01
PEFR	333.43±03	305.5± 20.07	0.01
Symptom Score	70.6%± 4.24	65.2%± 5.10	0.01

Table (4):- FVC1, FEV1 and Symptom Score of Montilucast+ Desloratidine and Placebo after treatment

Parameter	Montilukast+ Desloratidine	Placebo	P value
FEV1	2.81 ± 0.17	2.39 ± 0.22	0.001
PEFR	348.3 ± 31.94	313 ± 16	0.001
Symptom Score	73 ± 3.31	65.2 ± 5.10	0.001

Table (5):- FEVI, PEFR, and Symptoms score of montilukast and Montilukast+ Desloratidine

Parameter	Montilukast	Montilukast+ Desloratidine	P Value
FEVI	2.75 ± 0.23	2.81± 0.17	0.001
PEFR	333.43 ± 22.02	348.8 ± 31.94	0.001
Symptoms Score	70.6 ± 4.24	73 ± 4.35	0.001

Discussion

Asthma is one of the most common diseases for which there is no curative therapy. Steroids have been recognized as the most powerful anti inflammatory agents used for treatment of acute exacerbation and prevention of attacks, however steroids have well known for their serious side effects. Cysteinylleukotriens are important proinflammatory and bronchoconstrictor mediators in the

pathogenesis of asthma, while leukotriene receptor antagonists demonstrate hybrid anti-inflammatory and bronchodilatory properties.[14]. Desloratidine is a second generation antihistaminics. It is the principal metabolite of Loratidine, it is orally active none sedating peripheral H1 receptor antagonist. It is indicated for the treatment of seasonal allergic rhinitis, perennial allergic rhinitis and chronic idiopathic urticaria.[15]. This study has been designed to evaluate the possible role of Montilukast alone and Montilukast plus Desloratidine in the treatment of mild and moderate Asthma. One hundred and fifty patients who are age and gender matched were enrolled in this study. The differences between the measured parameters at the start of treatment were statistically insignificant, however the differences between the measured parameters after 3 months of treatment with montilkust in comparison to placebo was statistically significant, ($p \leq 0.01$). This result is in agreement with a study done by Theodore.[16] who found that montilukast, compared with placebo significantly improve asthma control during after 12 weeks treatment period, and MJ Noonan.[17] who found a significant dose related improvement in chronic asthma with Montilukast treatment. In a meta analysis study performed by Barnes et al[18]which have identified seven double-blind, randomized, placebo-controlled studies of adult patients with mild-to-moderate chronic asthma in which montelukast was investigated. This subgroup analysis indicate that montelukast produced improvements in parameters of asthma control in patients with mild persistent asthma, however the statistical differences although it was significant ($p \leq 0.02$) but it was less significant than in our study ($p \leq 0.01$).This difference may be due to the fact that this study is a meta analysis of 7 different studies which has been done on patients with only mild asthma with near normal lung function and the treatment period Was shorter than in this study. Longer periods of treatment of asthmatic patients with both Montilukast plus desloratidine have resulted in further improvement of the measured parameters with highly significant differences ($p \leq 0.001$). Few studies have been reported in the literature which studied the effect of combinations of leukotrien antagonists with a second generation antihistaminics in asthmatic patients. A study done by Richter K et a.[19] showed that the combination of azelastine and montelukast in clinically recommended doses has a greater effect in suppressing early and late allergen reactions in asthmatic patients than each drug alone. The effect of combination of lekotriene antagonist (Zafirlukast) and the antihistaminic (Loratidine) was significantly ($p < 0.05$) more effective than either drug used alone during the late asthmatic reaction.[20]Both cysteinyl- leukotrien and histamine has been found to be the predominant mediators of allergen induced airway obstruction of asthmatics both in vitro and in vivo.[21] and it has been demonstrated that leukotrienes and histamine together mediate the major part of both the early asthmatic reaction and the Late Asthmatic Reaction following exposure of asthmatics to allergen.[21]The recent development of H1-receptor antagonists devoid of clinical sedative effects has enabled the administration of doses of H1-antihistamines which achieve a greater degree of H1-receptor blockade within the airways, thus permitting a better appraisal of the role of histamine in this condition. Furthermore, the receptor specificity of many of these

agents has been focused such that terfenadine, astemizole, loratadine and cetirizine are devoid of anticholinergic activity and exhibit little alpha-antagonistic or anti-serotonin activity of clinical relevance. However, of these agents both loratadine and cetirizine possess additional actions likely to be of relevance to asthma.[22] Combination of leukotriene antagonism and antihistamines may represent a new strategy for treatment of airway obstruction in asthmatic patients. From this study we conclude that the combination of leukotrienes antagonist and second generation antihistaminics has a synergistic actin in the treatment of bronchial asthma, further studies are needed to evaluate other types of the new generations of antihistaminics with and without the addition of leukotriens antagonist in the treatment of asthma.

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