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A comparison between effects of two medications on asthmatic child

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Abstract
Background: Asthma is a common chronic illness of childhood and it is the leading cause of childhood morbidity as measured by school absence, emergency department visit and hospitalization. All children with persistent asthma are in need for controller therapy. Beclomethasone dipropionate inhaler is corticosteroid medication used as controller of persistent asthma. Montelukast is a leukotrine receptor antagonist used as second line in controlling the symptoms of asthmatic child.
Objective: comparison between the effects of beclomethasone dipropionate inhaler and montelukast on the total serum level of immunoblobulin E and Childhood Asthma Control Test in asthmatic children aged 4 -11 years.
Methods: A randomized clinical trial was done in Children welfare Teaching Hospital from August 2017 to the end of October 2018. Ninety-seven patients were collected from asthma outpatient clinic aged 4-11 years with mild persistent asthma and randomly divided into beclomethasone group (51) patients and montelukast group (46) patients, the total serum IgE was done before initiation of treatment and another reading was done after 3 months. The score of symptoms control was evaluated by Childhood Asthma Control Test C-ACT after 1 month of treatment and another evaluation was done 2 months later.
Results: There was significant reduction in total serum IgE level (21% for montelukast group and 27% for beclomethasone group after 3 months of treatment compared to base line IgE and there was significant improvement in Childhood C-ACT scores (16% for montelukast group and 24% for beclomethasone group) after 3 months of treatment compared to first month of treatment. There was significant improvement in beclomethasone group compared to montelukast group after three months of treatment.
Conclusions: Both beclomethasone and montelukast are effective controllers for asthma symptoms and reducing total serum IgE level. Beclomethasone is better than montelukast in improving C-ACT scores.

Keywords: Asthma, beclomethasone, montelukast, Ige

Introduction
Asthma is defined as "chronic inflammatory disorder of the airways in which many cells and cellular elements play a role, in particular, mast cells, eosinophils, T lymphocytes, macrophages, neutrophils, and epithelial cells. In susceptible individuals, this inflammation causes recurrent episodes of wheezing, breathlessness, chest tightness, and coughing, particularly at night or in the early morning. These episodes are usually associated with widespread but variable airflow obstruction that is often reversible either spontaneously or with treatment. The inflammation also causes an associated increase in the existing bronchial hyper responsiveness to a variety of stimuli" [1].
Asthma affects approximately300 millions people (7-10% of the population) around the world, with increasing prevalence in most countries, especially among children [2].

Childhood Asthma
Although asthma affects people of all ages, it most often starts in childhood. Pediatric asthma differs from adult asthma in many ways. Differences mostly observed regarding epidemiology, diagnosis, treatment and prognosis of the disease [3]. The prevalence of childhood asthma is more than adult asthma in most countries [4].

Epidemiology

Childhood asthma is a common chronic disease and continues to be the leading serious chronic illness among children [5]. The prevalence is widely variable in different countries. The International Study of Asthma and Allergies in Childhood (ISAAC) recorded the prevalence of childhood asthma in 97 countries and found a wide range in prevalence, from 0.8% to 37.6%. Furthermore, childhood asthma is common in developed countries and is strongly linked with other allergic conditions. In contrast, children living in rural areas of developing countries are less likely to develop asthma and allergy [6]. In Iraq ISAAC recorded the prevalence of childhood asthma as 16.3% in primary school children (6).childhood asthma is the most common cause of childhood emergency department visits and hospitalizations in the united states. About 8.9 million of US children (12.2%) were diagnosed with asthma and boys are more likely to have asthma than girls with ratio of 1.4:1 [7]

Immunoglobulin E

Immunoglobulin E is involved in allergic inflammation, especially in early-phase response, but it also involved in late-phase allergic response and the development of chronic allergic diseases [8]. Advances in the role of IgE in allergic inflammation have been made with the development of monoclonal antibody to IgE (omalizumab) that reduces IgE levels, thereby reducing allergic inflammation [9]. In patient with allergic asthma anti-IgE therapy with omalizumab reduces serum IgE levels and down-regulates expression of IgE receptors on mast cells and basophils. In the airways, omalizumab causes a profound reduction in tissue eosinophilia, together with reductions in submucosal T-cell and B-cell numbers [10].

IgE Synthesis

The induction of IgE synthesisrequires twosignals. The first signal initiates IL-4 or IL-13 activation of germline (a messenger RNA) transcription at the epsilon (ε) immunoglobulin locus, which dictates isotype specificity. The second signal involves the engagement of CD40 on B cells by CD40 ligand expressed on T cells [11].

IgE Receptors

The IgE mediated allergic response depends on the ability of IgE to bind selectively to Fc epsilon receptors (FcεR) on various inflammatory cells [12]. Fc epsilon receptors are tyrosine kinase receptors of two major types [13]: FcεRI (type I Fcε receptor or the high-affinity IgE receptor) found on the surface of mast cells, basophils, dendritic cells and eosinophils FcεRII (type II Fcε receptor or the low-affinity IgE receptor), also known as CD23, found on B cells, eosinophils, platelets, and dendritic cells.

IgE Serum levels

Total serum IgE (TSIgE) was found to be gradually increased throughout childhood, with a peak at 8-12 years of age. Age specific IgE reference values were [14]:

- Cord blood: 0.06 -6.83 IU/ml.
- < 1 year: 0.35 -6.6 IU/ml.
- 1-2 years: 3.8 -20 IU/ml.
- 2-5 years: 16.0 -25 IU/ml.
- 5-8 years: 26.2 -46.1 IU/ml.
- 8-12 years: 34.6 -75.5 IU/ml.
- 12-16 years: 26.3 -65.8 IU/ml.

Elevated TSIgE levels are seen in patients with atopic diseases, with the highest levels seen in patients with both asthma and atopic dermatitis, followed by atopic asthma alone, atopic dermatitis alone, and allergic rhinitis [15]. An extremely elevated level is characteristic for allergic bronchopulmonary aspergillosis. Elevated TSIgE levels are also seen in other disorders, including parasitic infections (e.g. strongyloidiasis, ascariasis and schistosomiasis), non-parasitic infections (e.g. HIV and Tuberculosis), hematologic malignancies and primary immunodeficiency diseases like hyper-IgE syndrome. Slightly elevated levels are also detected in smokers and in those with alcoholism [16].

In allergic asthma, TSIgElevel can be used as a biomarker for monitoring response to therapy [17]. Also it is helpful to differentiate between atopic and non-atopic asthmatics prior to allergen-specific IgE determination [18]. Many studies demonstrated that TSIgE levels reflects the severity of asthma in both children and adults and Serum IgE levels were increased as the severity of asthma increased [19]

Inhaled corticosteroids (ICSs)

Inhaled corticosteroids are the most effective controller therapy for asthma in children of all ages. Corticosteroids are the most potent anti-inflammatory drugs currently available for the treatment of asthma. The broad action on the inflammatory process accounts for their efficacy as preventive therapy. The anti-inflammatory effects are mediated through binding to steroid receptors that modulate inflammatory gene expression [20]. Corticosteroids block late-phase reaction to allergen, suppress the generation of cytokines and release of inflammatory mediators and inhibit inflammatory cell migration and activation [21].

Beclometasone dipropionate

Beclomethasone diproionate is a steroid medication. It is available as an inhaler, cream, pills, and nasal spray. The inhaled form is used in the long-term management of asthma, the cream may be used for dermatitis and psoriasis, the pills have been used to treat ulcerative colitis and the nasal spray is used to treat allergic rhinitis and nasal polyps [22]. Treatment in children aged ≤5 years generally produces similar clinical effects as in older children, but dose-response relationship is less clear. The clinical response may differ depending on the inhaler and the child's ability to use the inhaler correctly. With use of a spacer device, medium daily dose of this usually results in near maximum benefits in the majority of patients [23]. The clinical benefits for children with intermittent, viral-induced wheeze remain controversial. There is no evidence to support the use of maintenance low-dose ICS therapy for preventing early transient wheezing [24]. Adverse effects are closely related to the dose of particular drug. Other factors include duration of therapy and oral bioavailability. Minimum side effects (mostly local) are observed with daily low-dose therapy, while serious systemic adverse effects (like Suppressed growth velocity and hypothalamic-pituitary-adrenal axis suppression) are usually associated with long term daily high-dose therapy [25]. The potential side effects of ICS therapy in children include the following [26].

Local side effects: Oropharyngeal candidiasis, dysphonia, sore throat, pharyngitis, reflex cough and bronchospasm.

Systemic side effects: suppressed growth velocity, hypothalamic-pituitary-adrenal axis suppression, reduced bone mineral density, osteoporosis, bone fractures, increased susceptibility to infections, cataracts, glaucoma, and skin thinning and bruising.

Leukotriene

Modifiers Leukotriene modifiers include leukotriene receptor antagonists (LTRA) and a 5-lipoxygenase inhibitor that are available as oral controller drugs for the treatmentof pediatric asthma [27]. Two cysteinyl-leukotriene 1-receptor antagonists are available, montelukast (for patient's ≥1 year of age) and zafirlukast (for patient's ≥7 years of age). The 5-lipoxygenase inhibitor zileuton is available for patient's ≥12 years of age [28]. Montelukast: Montelukast is a leukotriene receptor antagonist available as sodium salt. Chemically, montelukast sodium is: Sodium 1-[({(R) -m -[(E) -2 -(7-chloro -2 -quinolyl) -vinyl] -α [o-(1-hydroxy -1 -methylethyl) phenethyl] -benzyl} thio) methyl] cyclopropaneacetate. The chemical structure is shown in figure (4) [29].

Mechanism of Action

Montelukast blocks cysteine-leukotriene 1 receptor (Cys-LT1), thereby preventing the biological effects of the cysteine leukotrienes (Cys-LTs) LTC4, LTD4and LTE4 [28]. The Leukotrienes Pathway Leukotrienes (LTs) are eicosanoids derived from arachidonic acid (AA). Activation of phospholipase A2 results in the release of AA from cell membrane. Free AA can be converted by cyclooxygenase (COX) to form prostanoids (prostaglandins and thromboxane) or converted via the 5-lipoxygenase (5-LOX) pathway to form LTs. The AA is presented to the 5-LOX enzyme by the 5-LOX-activating protein (FLAP) and converted sequentially to 5-HPETE (5-hydroperoxyeicosatetraenoic acid) and then to LTA4(71).The 5-LOX pathway results in the formation of a non-peptide leukotriene (LTA4) which is either converted enzymatically to LTB4or conjugated with glutathione to produce Cys-LTs LTC4, LTD4and LTE4. LTC4isactively transported extracellular, where subsequent cleavage of amino acids yields LTD4and LTE4. Cys-LTs are degraded rapidly in the extracellular space with a very short half-life. LTE4undergoesbiliary and urinary excretion [30].

Leukotrienes are synthesized from cell membrane phospholipids in response to a variety of biologic signals including antigen challenge of sensitized tissues. Cys-LTs are produced both by constitutive cells in the lungs (mast cells and alveolar macrophages) and by infiltrating cells (eosinophils). LTB4is predominantly produced by neutrophils [31].

Aim of the Study

To evaluate the effects of montelukast on patients with mild persistent asthma in comparison with inhaled beclomethasone.

Patients and Methods

A randomized clinical study was done in Children welfare Teaching Hospital /Medical city complex 1st of August 2017 to the end of October 2018 and our patients were collected from asthma outpatient clinic of the hospital study was included on 104 patient, seven of them didn`t complete the study (because of lack of contact) and the patients were interviewed using specialized questions specially designed for this study included name of the patient, age, address, medications used previously, number of admissions to the hospital due to asthma, animal contact, smoker contact, weight and height. Assessment of asthma severity was done for each patient.

Patient's selection

Inclusions criteria: include the followings

1. Asthmatic patients.
2. Age 4 -11 years.
3. Mild persistent asthma.

Exclusions criteria

1. Patients on controller therapy.
2. Patients who received systemic corticosteroids therapy one week before this study.
3. Patients with other chronic disease.
1. Patients assessment and follow up: Included the following :-

IgE assessment: Determination of total serum IgE level was performed by TOSOH AIA-360 Analyzer (an automated immunoassay analyzer) using a ready -made kit (ST AIA-PACK IgEII) for this purpose.

Childhood Asthma control test C-ACT

Asthma control test consists of 7-questions, 2 part questionnaire, with one part to be completed by the child (4 questions referring to the present condition) and the other part to be answered by the parents (3 -31-questions referring to the past 4 weeks).It is designed to be use by patients aged 4-11 years and scored by summing responses for each of 7 items to produce final score ranging from (0-27).

A score equal or less than 19 points indicates that a patient`s asthma is not controlled, this score evaluated 1 month after initiation of treatment and then re-evaluated 2 months later. An interview was done with each patient and parent separately, the steps in C-ACT shown in figure (2) was followed by translation to Arabic language and then the score was calculated for each patient.

Statistical analysis

Collected data were analyzed using SPSS version 20.0 for windows (SPSS Statistics, IBM, USA) and the results were expressed as mean ± standard deviation (SD).Differences of means within groups were examined by paired sample t-test. P values < 0.05 were considered as statistically significant

Results

Ninety seven patients (their ages between 4 -11years) completed the study, 51 patients were received inhaled beclomethasone and 46 patients received montelukast for 3 months. Seven patients (3frombeclomethasone group, 4 from montelukast group) didn't complete the study. Baseline Characteristics for the patients who completed the study are given in (table 1) and show no significant difference in both groups.

Table 1: Patients baseline characteristics

	Montelukast group number = 46	Beclomethasone group number =51	p. value
Male (%)	58.6%	51%	<0.05
Age (years)	7.1 ± 1.	86.4±1.8	<0.05

Effects of treatment with montelukast and beclomethasone on total serum IgE levels in asthmatic children. Table (2) showed the following results:

At the beginning of the study, serum levels of total IgE did not differ among the beclomethasone and montelukast groups (p.value > 0.05) (table 2). After 3 months of treatment, there was highly significant reduction (P<0.01) in total serum IgE levels for patients treated with montelukast or inhaled beclomethasone (21%) and (27%) respectively, compared to baseline levels. There was no significant difference (P>0.05) in total serum IgE levels between patients in montelukast and beclomethasone groups after treatment.

Table 2: Effects of treatment with inhaled beclomethasone and montelukast on total serum IgE levels in children with asthma

Group	Number of patients	Total serum IgE (IU/ml)		p.value
		Baseline	After treatment	
beclomethasone	51	1540.5 ± 639.2	1124.1 ±551.4	<0.01
Montelukast	46	1414.9 ± 945.9	1122.8 ±754.6	<0.01
p.value		Ns	Ns	

Ns=Not significant

Effects of treatment with montelukast and inhaled beclomethasone on C-ACT scores in children with asthma

Table (3) presented the following results: At the end of 1stmonth of treatment, there was no significant difference (P>0.05) in C-ACT scores between patients in montelukast and beclomethasone treatment groups. At the end of 3rd month of treatment, there was highly significant increase (P<0.01) in C-ACT score for patients treated with montelukast and beclomethasone (16%) and (24%) respectively, compared to score after 1 month.

There was highly significant difference (P<0.01) in C-ACT between patients in montelukast and beclomethasone groups after treatment

Table 3: Effects of treatment with beclomethasone and montelukast on C-ACT scores in children with asthma during the treatment period.

Group	Number of patients	C-ACT scores		p. value
		1st month of treatment	3rd month of treatment	
beclomethasone	51	19.8±124.	6 ±1.6	<0.01
Montelukast	46	4620.4±0.9	23.5±1.1	<0.01
p.value		Ns	<0.01	

Discussion

The current study aimed to assess the effect of montelukast versus beclomethasone on the total serum IgE level and asthma control test in children aged 4-11years. The age and gender distribution was not significantly different between both treatment groups (beclomethasone andmontelukast) which indicated adequate randomization and assignment of patients to receive the medication. Regarding the effects of treatment with montelukast and inhaled beclomethasone on the total serum IgE level in asthmatic children, the present study found that both treatments had significantly reduced the levels of total serum IgE compared to its level at baseline. The mean serum level of total IgE was significantly reduced by (27%) in beclomethasone group, and significant reduction by (21%) in montelukast group.

However, despite the reduction was larger with inhaled beclomethasone than montelukast, the differences in the mean total serum IgE level was statistically insignificant between both groups neither at baseline nor after three months, these findings indicated that the effect of montelukast on the total serum IgE level was approximate that of inhaled beclomethasone. These findings agreed that reported in previous studies that compared the effect of these two drugs on the total serum IgE level, In an Italian study, Scaparrotta reported that inhaled corticosteroids and montelukast significantly reduced the serum levels of total and specific IgEin asthmatic children aged 5-11 years [32].

Similar findings were also reported in an Iranian study conducted by Razi and Mossave who found a significant improvement in the symptoms and reduction in the circulating total and allergen specific IgE level in asthmatic children aged 6-12 years [33].

It is well-known that pivotal to the pathophysiology of allergic illnesses the allergen binding to IgE on the effector cells surfaces that lead to discharge of pro-inflammatory mediators, therefore, inhibition of IgE represent a treatment that will improve IgE-mediated allergic reactions and will reduce asthma symptoms [12].

The current study found a significant improvement in the C-ACT scores after 3 months of treatment (16% improvement in montelukast group and 24% improvement in beclomethasone group compared to 1st month of treatment), on the other hand a statistically significant difference between both groups had been found at three months, where the mean C-ACT score was significantly higher in beclomethasone group than in montelukast group.

In an Egyptian study, Ahmed M. AbdelRazik reported that both inhaled beclomethasone(the dose used was 600mcgand montelukast (the dose used was 5mg)improved asthma symptoms score after 3 and 6 months of treatment and found that inhaled beclomethasone superior to montelukast at this point.

At another point of our study, there was parallel improvement in Asthma Control test in the patient who had

reduced total serum IgE level after treatment in both groups; this indicates that the treatment which reduce total serum level of IgE would improve asthma control by improvement of IgE allergic reactions as reported in Ahmed M. Abdel Razik [34].

Regarding the safety of both montelukast and beclomethasone, fortunately, the current study did not reported any obvious adverse effect or intolerability associated with the use of these two drugs, and none of our patients withdrawn due to adverse effect.

These findings consistent with the general pharmaceutical characteristics of the studied drugs as both were FDA documented to be safe agents in treatment of asthma. Nonetheless, our findings disagreed the previous study of Elliot *et al*., who reported adverse experiences in more than 5% of their cases and these adverse effects included respiratory tract infection, headache, and sinusitis, this discrepancy between our study and that of Elliot [35], might attributed to the difference in sample size.

Conclusions

1. Both chewable montelukast and inhaled beclomethasone had significantly improved asthma control after three months of treatment and both drugs were effective in reducing the total serum IgE level in asthmatic children.
2. Inhaled beclomethasone at dose of 500mcg /day was significantly better than montelukast in improving asthma control.
3. Both treatments were safe and tolerable and no obvious adverse effects had been reported.

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