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In children, asthma is the most common cause of school absence, affecting children's educational potential and adversely affecting a child's quality of life (Rance and Trent, 2005) and associated with significant morbidity and economic burden (Global Strategy for Asthma Management and Prevention, 1995).

The diagnosis of asthma is based on recurrence of symptoms remission and symptom responsiveness to bronchodilator and/or anti-inflammatory agents (Bradley and Katie, 2009). Wheezing in infancy is found to be an important risk factor for the development of asthma (Csonka, 2001).

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Therapeutic and Some Biochemical Studies of Montelukast and Ketotifen of Children with Mild Asthma

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I. Introduction

Asthma is the most common chronic disease of childhood and its prevalence has substantially increased worldwide, particularly in pre-school children (Masoli *et al.*, 2004). According to many investigators asthma prevalence is above 10% in most developed countries & expected to be twice in 2020 (Movahedy, 2000;Tepas *et al.*, 2001, Liu *et al.*, 2004, Lodrup *et al.*, 2006).

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The diagnosis of asthma is based on recurrence of symptoms remission and symptom responsiveness to bronchodilator and/or anti-inflammatory agents (Bradley and Katie, 2009). Wheezing in infancy is found to be an important risk factor for the development of asthma (Csonka, 2001). It is generally recommended that below the age of 3 years, three or more wheezing episodes should be diagnosed asthma (Anon, 1992). Among children older than 3 years, the diagnosis of asthma becomes progressively more clear & beyond 6 years of age the definition of the National Heart, Lung and Blood Institute becomes logical which states that: asthma is primarily a disease of air way inflammation in which eosinophils, mast cells and release of inflammatory mediators as cytokines and leukotrienes from these cells are prominent, producing recurrent episodes of cough & wheeze often associated with increased bronchial hyperresponsiveness & reversible airway limitation (Barnett *et al.*, 1997; Anon, 1998).

The main purpose of asthma treatment is allowing the child to have a life with normal pulmonary function. Pulmonary function tests (PFTs) are used to determine asthma severity along with clinical symptoms and medication requirements. Normal lung function is one of the goals of asthma management in international guidelines, which includes forced expiratory volume in 1 second (FEV1), forced vital capacity (FVC) and peak expiratory flow (PEF) (Beydon *et al.*; 2003).

In children, preventive treatment has become the cornerstone of management of asthma & emphasis in health care has moved from treatment in acute illness to prevention and control of chronic conditions (Bateman *et al.*, 2008).

Drugs stated in the global international asthma (GINA 2006) as prophylactic medications are: slow-release theophylline, long acting beta2 agonist, ketotifen, oral corticosteroids, inhaled corticosteroids, and nedocromil, cromoglycate, & leukotriene modifiers (Paulo *et al.*, 2003).

The two classes of drugs most commonly used for childhood asthma, namely the β2-agonist bronchodilators and inhaled corticosteroids, have both come under increasing inspection (Lipworth, 1993; Nishima *et al.*, 2005).

As the development of tolerance resulting from continuous use of β2-agonists is of concern and the risk of adverse systemic effects with inhaled corticosteroids, particularly in children require high dosages. In addition, ensuring adequate compliance with inhaled therapy continues to be a major difficulty. For these reasons, an orally active, once-daily, disease-modifying drug with additional bronchodilator properties would provide a major advance for managing young patients with asthma (Warner, 2001). Leukotriene antagonists have witnessed a favorable preference in asthma management of children as they target a specific site in the inflammation cascade of asthma (Riccioni *et al.*, 2004).

Montelukast is an oral leukotriene receptor antagonist, licensed as add on therapy for the treatment of 6 years or older patients , with mild to moderate asthma inadequately controlled on 'as required' short-acting beta2-agonists and inhaled corticosteroids and for prophylaxis of asthma in which the predominant component is exercise-induced broncho-constriction (Rabe and Schmidt, 2001).

Montelukast is recommended for use in 2 to 4 year age group for whom long acting beta2-agonists such as salmeterol are unlicensed or those poorly controlled on short-acting beta2-agonists and inhaled corticosteroids. Montelukast may offer an alternative to theophylline as add-on therapy in asthma poorly controlled by short acting beta2-agonists and inhaled corticosteroids alone (Naomi *et al.*, 2006).

Montelukast is given orally & is palatable by children in its formulations thus drug delivery and compliance should be better than for inhaled

medications, especially in children, in whom low rates of compliance with inhaled corticosteroids are associated with exacerbation of disease (Milgrom *et al.*, 1996).

Numerous actions of histamine exhibits relevance to asthma, such as bronchoconstriction, enhanced mucus secretion and increased vascular permeability. These actions are partly H1-receptor mediated (Howarth, 1990).

Ketotifen is antihistamine; non bronchodilator prophylactic drug used in asthma for its mast cell stabilizing effects. It is now widely used in some countries to control symptoms, improve lung function and reduce bronchodilator requirements in children when used regularly for 6–12 weeks (Rackham *et al.*; 1989; Grant *et al.*, 1990; Kurosawa, 1990).

With attention to increased asthma prevalence as a common and chronic illness and its unpleasant outcomes, asthma control is important by preventing its complications in young children. Thus, the purpose of the present study was to compare the efficacy and safety of montelukast & ketotifen as controller in the treatment mild persistent asthmatic children.

II. Review of Literture

Asthma

1.1 : Definition

The latest definition as stated by GINA 2009 of asthma; asthma is a chronic inflammatory disorder of airway in which many cells and cellular elements play a role. The chronic inflammation is associated with airway hyperresponsiveness that leads to recurrent episodes of wheezing, breathlessness, chest tightness, and cough particularly at night and early morning (Figure 1-1). The main physiological feature of asthma is episodic airway obstruction characterized expiratory airflow limitation (GINA, 2006). The various pathophysiologic mechanisms and clinical manifestations of asthma make it difficult to formulate a clear-cut definition. However, the whole concept of asthma definition as a distinct disease has been challenged (Silverman & Wilson, 1997). It has been proposed that asthma is probably not "a single disease, but rather a complex of multiple separate syndromes that overlap (Wenezel, 2006).

Asthma is much more likely to involve acute and severe episodes in children than in adults & tend to develop in a few days or even hours. Asthma is often initiated by a viral infection, and prompt, effective treatment is necessary to prevent frequent visits to the emergency department or readmissions to hospital (Levison, 1991). Respiratory syncytial virus (RSV) is the most important cause of viral lower respiratory tract illness in infants and children worldwide and is responsible for over 120000 annual hospitalizations in infants in the US alone (Chávez-Bueno *et al.*, 2006). The diagnosis may be more difficult in children than in adults, since young children are unable to undergo pulmonary function and bronchial provocation test (Pellegrino *et al.*, 2005).

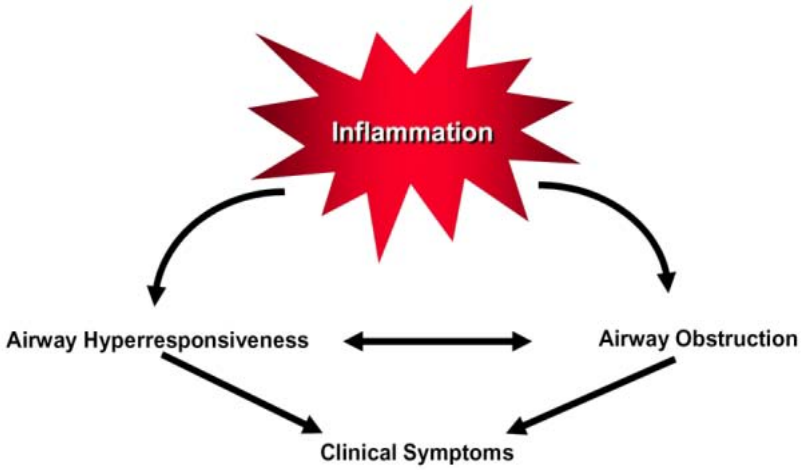

Figure 1-1: The interplay and interaction between airway inflammation and clinical symptoms and pathophysiology of asthma.

1.2 : Types of Asthma and Their Clinical Features

There are three forms of asthma known, for all of which the underlying causes have not been entirely elucidated.

1. Allergic asthma: Also known as extrinsic asthma may begin during childhood and persist into adulthood. It is linked to an immune response, as is the case with allergic reactions (Barnes, 2000).
2. Non-allergic asthma: referred to as intrinsic asthma is considered late-onset asthma, presenting typically during adulthood. It is triggered by factors unrelated to allergies and the resulting symptoms at

typically during adulthood. It is triggered by factors unrelated to allergies and the resulting symptoms at least partially reversible with medication are not associated with an allergic reaction, meaning it is not considered an immune response (Asthma and Allergy Foundation of America, 2002).

3. Occupational asthma: is typically associated with exposure to fumes, gases, and dust or other substances harmful to the airways while working, causing onset, or recurrence of asthmatic symptoms. Occupational asthma can be either allergic or non-allergic in nature, and can be more prevalent in persons with a previous family history of allergies or asthma (Malo and Chan-Yeung, 2009).

Typical symptoms are similar across all forms of asthma and generally include wheezing, shortness of breath, chest tightness, coughing, as well as potential runny nose, nasal congestion and eye irritation, depending on the severity and form of the asthma attack. Severity of this disease varies by the individual, and requires equally diverse treatment options that meet the medical needs of each asthmatic (Diette *et al.*, 2004).

1.3 : Prevalence of asthma

Asthma is a common affliction of the population, present throughout the ages. The history of asthma is still not well defined but can occur at any time & it is principally a pediatric disease, with most patients being diagnosed by 5 years of age & up to 50% of children having symptoms by 2 years of age (NHLB, 1997).

In the US & in other western industrialized countries, the prevalence of asthma in children has reached epidemic proportion & that the rate in children younger than 5years has increased 16%. About 30-70% children with asthma will improve markedly or become symptom free by early childhood; however chronic disease persists in about 30-40% of patients & generally 5% or less develops severe chronic disease (Gustafsson *et al.*, 2006).

1.4 *: Causes of asthma*

Although the causes of asthma are not completely understood, but the following are factors related to asthma occurrence:

1.4.1: Genetic

Genetic linkage has been identified in loci containing major genes that can influence atopy and asthma (Cookson and Moffatt, 2000). Several asthma and allergy susceptibly genes have been identified through genome-wide linkage analysis (Holloway and Koppelman, 2007).

1.4.2 : Gender

The ratio of asthma prevalence is twice the amount of male to female up to 13 -14 years of age. The ratio then progressively reverses to a 2:1 ratio for woman to man (Schatz and Camargo, 2003). The reason might be that the lung size is smaller in males than females at a younger age but is larger in adulthood (Martinez *et al.*, 1995).

1.4.3 : Age

In most children, asthma develops before age 5 years, and, in more than half, asthma develops before they age 3 years.

Among infants, 20% have wheezing with only upper respiratory tract infections (URTIs), and 60% no longer have wheezing by age 6 years. Many of these children were called "transient wheezers" (Martinez *et al.*, 1995; Castro-Rodriguez, 2000). They tend to have no allergies, although their lung function is often abnormal.

These findings have led to the idea that they have small lungs. Children, in whom wheezing begins early, in conjunction with allergies, are more likely to have wheezing when they are aged 6-11 years. Similarly, children in whom wheezing begins after age 6 years often have allergies, and the wheezing is more likely to continue when they are aged 11 years (Lemnaske *et al.*, 2005).

1.4.4: Environment

The role of the exposure to environmental allergens in asthma development is not fully understood. The levels of exposure to house-dust mite, cat and dog dander were not related to childhood asthma, although sensitization to mite and cat allergens was associated with indoor allergen exposure (Lau *et al.*, 2000). Other epidemiologic studies have found that early exposure to dogs and cats may protect a child against allergic sensitization or the development of asthma (Gern *et al.*, 2004), although other studies do not suggest such relation (Remes *et al.*, 2001).

1.4.5: Tobacco smoke

Exposure to tobacco smoke increases the risk of asthma in children who have atopic dermatitis & aggravates symptoms of asthma, increases bronchial irritability and decreases pulmonary airflow rates (Murray and Morrison, 1989).

Studies of lung function after birth have shown that maternal smoking during pregnancy has a negative influence on lung development (Martinez *et al.*, 1995) & Parents of all such children should therefore be encouraged not to smoke. Passive and active smoking is associated with a reduced therapeutic response to corticosteroids reducing the likelihood of asthma being controlled (Strachan *et al.*, 1996; Withers *et al.*, 1998). Active smokers have more severe asthma symptoms, accelerated decline in lung function and impaired short-term therapeutic responses to corticosteroids (Strachan *et al.*, 1996; Chalmers *et al.*, 2002). The highest proportion of asthma related admissions to hospital are from smoking individuals (Thomson *et al.*, 2004).

1.4.6: Infections

The interaction between atopy and viral infections is complex. Reduced lung function and increased markers of inflammation observed before virus infection in the asthmatic patients with high levels of total IgE may be a risk factor for an adverse response to infection with rhinovirus (Zambrano *et al.*, 2003). Viruses have been shown to be potent triggers of asthma exacerbations, and the inability to restrict the symptoms of rhinovirus infections in the upper respiratory tract may be considered an indicator of asthma at all ages (Corne *et al.*, 2002). On the contrary to this, population-based studies assessing infections exposure in children for viruses have found that exposure to infectious agents protects against asthma (Yazdanbakhsh and Wahyuni, 2005). Most infants and young children who continue to have a persistent wheeze and asthma have high immunoglobulin E (IgE) production and eosinophilic immune responses in the airways and in circulation at the time of the first viral URTI. They also have early IgE-mediated responses to local aeroallergens.

1.4.7: Other causes of asthma

Oral antibiotics are frequently prescribed for upper and lower respiratory tract infections in children. Findings from epidemiologic studies have supported an association between antibiotic use in the first year of life and asthma development in early childhood (Kozyrskyj and Becker, 2005; Marra *et al.*, 2006). Evidence for this comes from that antibiotic administration causes altered intestinal flora, impaired barrier function, diminished Th-1 immune responses, and allergic airway disease, increased risk of childhood asthma.

1.5: Mechanism of asthma

The airway constriction that is characteristic of asthma is influenced by a number of physiological and environmental factors, including increased bronchial contractility, altered permeability of the bronchial mucosa, humeral and cellular mediators of inflammation, dysfunctional neural regulation and exposure to environmental stimuli as allergens (Phillips *et al.*, 1980). It involves several inflammatory cells and multiple mediators that result in characteristic pathophysiological change (Busse and Lemanske, 2001; Tattersfield, 2002).

1.5.1: Airway inflammation in Asthma

Airway inflammation in asthma is persistent even though symptoms are episodic, and relationship between the severity asthma and inflammatory intensity of asthma is not clearly established (Bousquet *et al.*, 2000; Cohn, 2004).

1.5.1.1: Inflammatory mediators

Inflammatory cells such as eosinophils, lymphocytes, and mast cells are abundant in asthmatic lungs. Multiple cytokines, including leukotrienes, have been found in bronchoalveolar lavage fluid of asthmatics. IgE antibodies are also linked to progression of lung disease (Busse and Lemanske, 2001).

Other constituent airway cells, such as fibroblasts, endothelial cells, and epithelial cells, that contributes to the chronicity of the disease. Finally, cell-derived mediators influence smooth muscle tone and produce structural changes and remodeling of the airway (Busse *et al.*, 1993; Henderson, 1994). Structural cells of the airways also produce inflammatory mediators, and contributed to the persistence of inflammation in various ways.

Inhaled antigen activates mast cells and Th2 cells in the airway. They in turn induce the production of mediators of inflammation (such as histamine and leukotrienes) and cytokines including interleukin-4 and interleukin-5. Interleukin-5 travels to the bone marrow and causes terminal differentiation of eosinophils (Figure 1-2). Circulating eosinophils enter the area of allergic inflammation and begin migrating to the lung by rolling, through interactions with selectins, and eventually adhering to endothelium through the binding of integrins to members of the immunoglobulin super family of adhesion proteins: vascular-cell adhesion molecule 1 (VCAM-1) and intercellular adhesion molecule 1 (ICAM-1). As the eosinophils enter the matrix of the airway through the influence of various chemokines and cytokines, their survival is prolonged by interleukin-4 and granulocyte-macrophage colony-stimulating factor (GM-CSF). On activation, the eosinophil releases inflammatory mediators, such as leukotrienes and granule proteins, to injure airway tissues. In addition, eosinophils can generate GM-CSF to prolong and potentiate their survival and contribution to persistent airway inflammation (Busse *et al.*, 1993).

In addition, generation of Th2 cytokines (e.g., interleukin-4 (IL-4), IL-5, and IL-13) could also explain the overproduction of IgE, presence of eosinophils, and development of airway hyperresponsiveness. There also may be a reduction in a subgroup of lymphocytes, regulatory T cells, which normally inhibit Th2 cells, as well as an increase in natural killer (NK) cells that release large amounts of Th1 and Th2 cytokines (Akbari *et al.*, 2006).

T -lymphocytes, along with other airway resident cells, also can determine the development and degree of airway remodeling. Although it is an oversimplification of a complex process to describe asthma as a Th2 disease, recognizing the importance of no. families of cytokines and chemokines has advanced our understanding of the development of airway inflammation (Barnes, 2002; Zimmermann *et al.*, 2003).

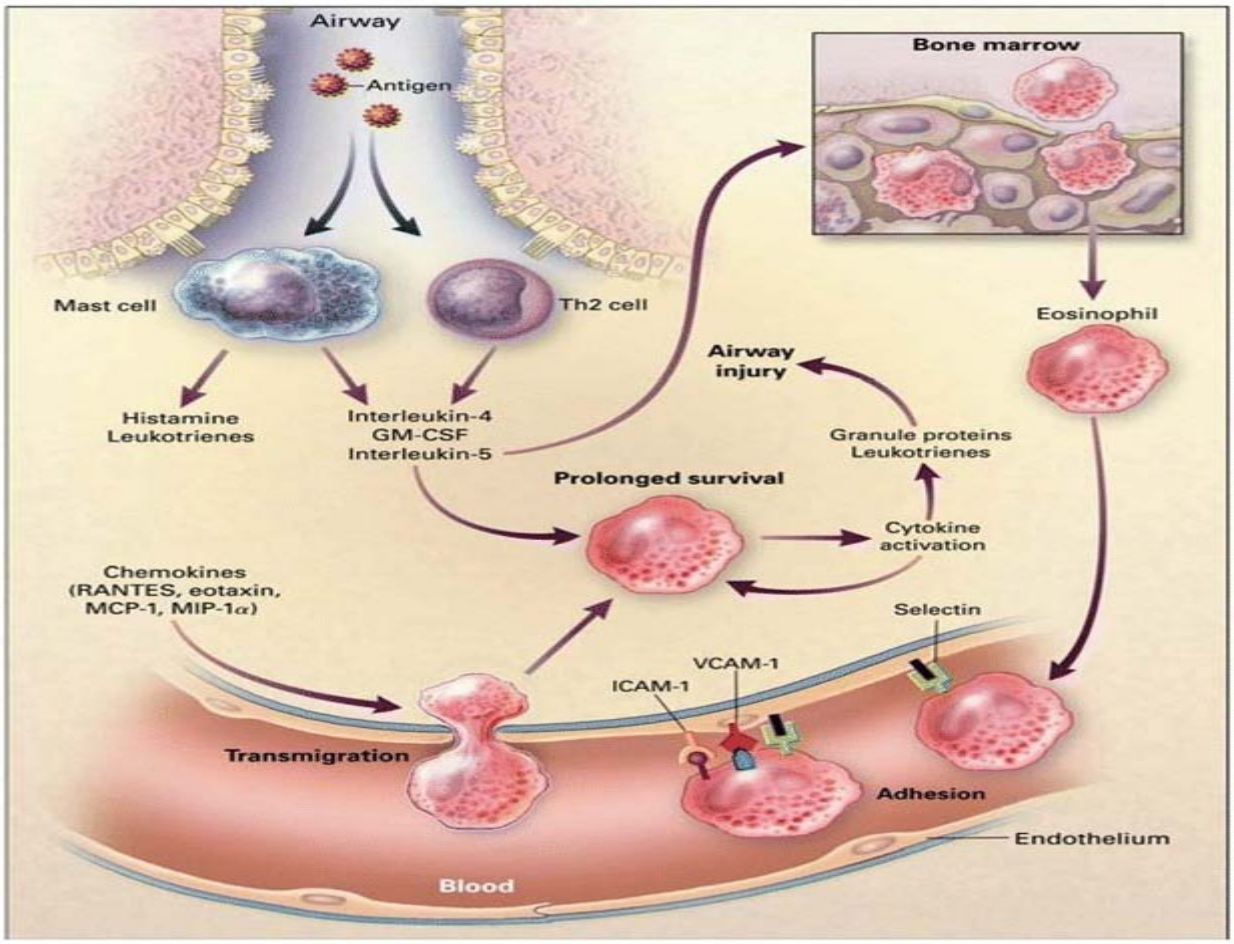

Figure 1-2 : Airway inflammation (Cohn *et al.*, 2004).

Vascular-cell adhesion molecule 1 (VCAM-1)
Intercellular adhesion molecule 1 (ICAM-1)
Granulocyte-macrophage colony-stimulating factor (GM-CSF)
Monocyte chemotactic protein (MCP-1)
Macrophage inflammatory protein (MIP-1α)

1.5.1.2: Immunoglobulin E

IgE is the antibody responsible for activation of allergic reactions and is important to the pathogenesis of allergic diseases and the development and persistence of inflammation. IgE attaches to cell surfaces via a specific high-affinity receptor. The mast cell has large numbers of IgE receptors; these, when activated by interaction with antigen, release a wide variety of mediators to initiate acute bronchospasm and also to release pro-inflammatory cytokines to perpetuate underlying airway inflammation (Sporik *et al.*, 2001; Boyce, 2003). Other cells, basophils, dendritic cells, and lymphocytes also have high-affinity IgE receptors.

The development of monoclonal antibodies against IgE has shown that the reduction of IgE is effective in asthma treatment (Castro-Rodriguez *et al.*, 2000; Busse and Lemanske, 2001; Holgate *et al.*, 2005). These clinical observations further support the importance of IgE to asthma.

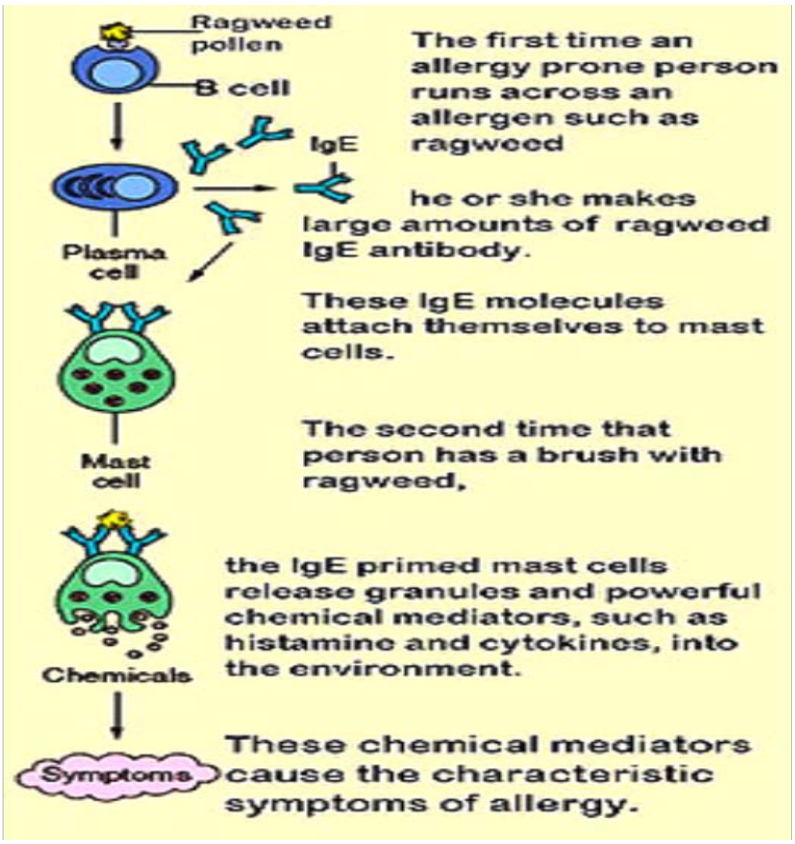

Figure 1- 3 : The role of IgE and mast cells in the development of allergy.

1.6: Diagnosis of asthma

Unlike other pulmonary diseases, asthma cannot be identified by a definitive pathologic picture or one diagnostic test. Rather, the diagnosis of asthma is based upon an appropriate clinical history and on pulmonary function tests (Enright *et al.*, 1994).

1.6.1: Clinical Diagnosis

1.6.1.1: Symptoms

A clinical diagnosis of asthma may be prompted by symptoms such as episodic short breathlessness, wheezing, cough and chest tightness (Levy *et al.*, 2006). Episodic symptoms after an incidental allergen exposure, seasonal variability of symptom recurrence and positive family history of asthma and atopic disease are also helpful diagnostic guide.

The following categories of symptoms are highly suggestive of a diagnosis of asthma: frequent episode of wheeze (more than once in month), activity induce cough or wheeze, nocturnal cough in period without viral infection, absence of seasonal variation of wheeze, symptoms persist after age 3 years (Guilbert *et al.*, 2006).

Di Lorenzo *et al.*, (1997) reported that there is an interrelationship of the allergen type, total serum IgE, eosinophil and bronchial hyperresponsiveness suggesting that all three may play a role in the development of bronchial asthma in rhinitis patients.

The mean serum IgE levels and peripheral eosinophil counts were nearly of the same range in controls and vasomotor rhinitis (VMR) cases. In allergic rhinitis (AR) the serum IgE levels were elevated during the acute symptoms, in associated sinonasal polyposis and fungal involvement. However, the peripheral blood eosinophil counts were not elevated in AR patients. In patients of rhinitis with asthma, the IgE levels and peripheral eosinophil counts were both elevated.

The measure of allergic status is of importance in order to establish the risk factors that can cause asthma symptoms in individual patients. The presence of allergens is measured by measure of IgE in serum (GINA, 2007).

1.6: Physical examination

1.6.2: Measurement of Air Flow Limitation

Measurement of lung function provides an assessment of the severity of airway limitation, its reversibility and variability and provides confirmation of the diagnosis of asthma (BTS, 2007).

There are different techniques for the detection of airflow limitation in the patient with asthma, of these methods is the use of spirometry (Enright *et al.*, 1994).

1.6.2.1: Forced expiratory volume in one second (FEV1)

Spirometry is the most frequently performed pulmonary function test and is an essential tool for the

diagnosis and follow-up of respiratory diseases (Vandervoode *et al.*, 2008).

The Forced Expiratory Volume in 1 second (FEV1) and the Forced Vital Capacity (FVC) are routinely used for this measure (Pellegrino 2005). The FEV1, which is the volume exhaled in the first second of expiration obtained from spirometry, is the measurement of lung volume during the execution of a forced expiratory maneuver.

The procedures and interpretation of FEV1 and Forced Vital Capacity (FVC) have been well codified (American Thoracic Society Statement, 1991; American Thoracic Society. Standardization of spirometry, 1995). Many lung diseases can result in a reduction of FEV1, thus a useful assessment of airflow limitation is the ratio of FEV1 to FVC. This ratio is usually greater than 0.75 to 0.80, but less suggests airflow limitation (Pellegrino *et al.*, 2005).

The ratio of forced expiratory volume in 1 second (FEV1) to forced vital capacity (FVC) may be more sensitive than FEV1 alone as an indicator of pediatric asthma severity (Carlos *et al.*, 2010). An FEV1/FVC >80% indicates well-controlled asthma in children aged 5-11 years.

1.6.2.2: Peak Expiratory Flow

The measure of Peak Expiratory Flow (PEF), using a peak flow meter, is important in both the diagnosis and the monitoring of asthma (American Thoracic Society Statement, 1991; U.S. Department of Health and Human Services, 1992; Smith *et al.*, 1992; American Thoracic Society, 1994; National Asthma Education and Prevention Program Expert Panel Report Number II 1997) although, The utility of PEF to detect the presence of airflow limitation is not particularly good, since the variability of PEF among individuals is very large (+30 percent)(Pennock *et al.*, 1983). However, PEF is a very useful method of monitoring changes or trends in the patient's lung function.

1.6.2.3: Exhaled nitric oxide levels

Levels of exhaled nitric oxide and carbon monoxide can also be used as "noninvasive" markers of airway inflammation (Kharitonov *et al.*, 1997). The levels of nitric oxide have been shown to be increased in asthma severity (Brindicci *et al.*, 2007).

1.7: Growth in asthmatic children

In 1940, Cohen observed that there was an association between asthma and growth inhibition, and that the persistence of allergic symptoms caused a retardation in stature and bone maturation.

Since then, many studies about the relationship between asthma and growth were carried out, and it is now known that, regardless of treatment, moderate and severe asthma cause a delay in the puberty stretch, which is caught up later on regarding adult height (Hauspie *et al.*, 1977; Preece *et al.*, 1986).

Early onset, duration and severity of the disease, chest deformity, hypoxemia, chronic anorexia, use of corticosteroids, and socioeconomic level are factors under study as potentially responsible for growth retardation, but the results have been conflicting (Cowan *et al.*, 1998).

Morbid processes also interfere with growth. Acute illnesses can cause its temporary arrest, and its posterior recovery will depend on how favorable the environmental, nutritional and socioeconomic conditions will be (Mata *et al.*, 1971; Floud *et al.*, 1990). As for chronic diseases, depending on the affected organs and systems, on the severity and duration of the disease, recovery may not occur at all (Mitchell *et al.*, 1995).

Growth charts show the weight status categories used with children and teens (Table 1-1).

Table 1-1: Age-weight status categories and the corresponding percentiles (Mei et al., 2002).

Weight Status Category	Percentile Range
Underweight	Less than the 5th percentile
Healthy weight	5th percentile to less than the 85th percentile
Overweight	85th to less than the 95th percentile
Obese	Equal to or greater than the 95th percentile

1.8: Classification of Asthma

To date, asthma severity has been classified according to the frequency of symptoms in combination with lung function parameters such as forced expiratory volume in one second and peak expiratory flow. The standard classification of asthma severity from the National Institutes of Health consensus guideline (Adapted from National Asthma Education and Prevention Program; 2002).

1.8.1: Mild intermittent asthma

These children have infrequent symptoms like cough and wheeze -- less than twice in one week. The episodes of asthma are short lived, and the child is well

between episodes. Lung function, if tested, is close to normal, and the child sleeps well, with night time symptoms not occurring more than twice in a month.

1.8.2: Mild persistent asthma

These children have symptoms of asthma - cough, wheeze, and breathlessness -- more than twice a week, but not daily. The acute episodes they have are likely to affect activity. They also have night time problems more than twice in one month. Though their lung function tests give near normal results, these children have reached a level of airway inflammation that requires ongoing treatment to control the disease and preserve lung function (Table1-2).

1.8.3: Moderate persistent asthma

These children have symptoms requiring reliever medication daily, and have night time symptoms at least once a week. Their activity is restricted, they have frequent school absences, and lung function tests are significantly abnormal.

These children have significant airway inflammation, and need inhaled steroids on a regular basis to keep their disease under control. Untreated, they have frequent exacerbations, and their lung function goes on deteriorating. Even when relatively well, controller therapy must be continued (Table 1-2).

1.8.4: Severe persistent asthma

Symptoms of asthma are almost continuous, and these children have severely restricted activity, frequent school absences and hospital admissions, and find it difficult to sleep through the night. The lung function test reports are grossly abnormal, and these children are unable to satisfy in much physical activity. These children need vigorous therapy, including high dose inhaled steroids, other long acting beta agonists, slow release formulations of theophylline, and leukotrienne modifiers (Table1-2).

All children with asthma must follow allergen avoidance measures. These will vary from child to child, depending on known triggers.

A child's asthma can improve or worsen with time, and frequent follow up with a specialist is necessary to step up or step down the treatment. A general principle is to start with a higher grade of treatment, and step down as the asthma comes under control.

Table 1-2: The standard classification of asthma severity from the National Institutes of Health consensus guideline.

Asthma classification*	Symptom frequency	Lung function†
Mild intermittent	Daytime: 2 days in a week or less Nighttime: 2 nights per month or less	PEF or FEV_1: 80 percent or more of predicted function
Mild persistent	Daytime: more than 2 days in a week, but less than 1 time per day Nighttime: more than 2 nights per month	PEF or FEV_1: 80 percent or more of predicted function
Moderate persistent	Daytime: daily Nighttime: more than 1 night per week	PEF or FEV_1: 60 to 80 percent of predicted function
Severe persistent	Daytime: continual Nighttime: frequent	PEF or FEV_1: 60 percent or less of predicted function

PEF = peak expiratory flow.
FEV_1 = forced expiratory volume in one second.
**—Clinical features before treatment or adequate control.*
†—Lung function measurements are used only in patients older than five years.
(Adapted from National Asthma Education and Prevention Program, 2002).

1.9: Asthma treatments in children

The current concept of asthma therapy according to the Global Initiative for Asthma (1995) is based on a stepwise approach, depending on disease severity, and the aim is to reduce the symptoms that result from airway obstruction and inflammation, to prevent exacerbations and to maintain normal lung function (Table 1-2).

1.9.1: Acute Therapy

Inhalation therapy is the cornerstone of asthma treatment in all age of children. In an acute asthma

exacerbation, inhaled beta2 agonists are a mainstay of treatment (Travers *et al.*, 2004). Oral corticosteroids given early during an acute asthma exacerbation (i.e., within 45 minutes of the onset of symptoms) reduce the likelihood of hospital admission (Rowe *et al.*, 2004). In addition, oral corticosteroids are more effective than inhaled or nebulized corticosteroids in children hospitalized with severe acute asthma (Edmonds *et al.*, 2004 Smith *et al.*, 2004).

Although theophylline is not widely used in the treatment of childhood asthma, there is some improvement of symptoms and lung function with the use of intravenous theophylline in children hospitalized with a severe asthma attack. However, this therapy does not reduce the length of stay or the need for additional bronchodilator treatment, and it is not recommended for routine use (Mitra *et al.*, 2004).

Beta2 – agonist

In an acute asthma exacerbation, inhaled $beta_2$ agonists are a mainstay of treatment. Administration of an inhaled $beta_2$ agonist via a metered-dose inhaler with a spacer device is equally as effective as nebulized therapy (Cates *et al.*, 2003).

There is no evidence to support the use of oral or intravenous $beta_2$ agonists in the treatment of acute asthma (Travers *et al.*, 2004). There is some evidence that high-dose nebulized $beta_2$ agonists administered every 20 minutes for six doses may be more effective than low-dose $beta_2$ agonists in treating severe acute asthma in children (Schuh *et al.*, 1989).

Corticosteriod

Oral corticosteroids are more effective than inhaled or nebulized corticosteroids in children hospitalized with severe acute asthma (Smith *et al.*, 2004). There is no evidence that intravenous corticosteroids are any more effective than oral corticosteroids in children (Adapted from National Asthma Education and Prevention Program, 2002).

A systematic review of additional studies in the emergency department—including three pediatric studies—demonstrated that inhaled corticosteroids in high doses reduce hospital admission rates in patients with acute asthma. However, there is insufficient evidence that inhaled corticosteroids alone are as effective as systemic steroids (Edmonds *et al.*, 2004).

Theophylline

Although theophylline is not widely used in the treatment of childhood asthma, there is some improvement of symptoms and lung function with the use of intravenous theophylline in children hospitalized with a severe asthma attack. However, this therapy does not reduce the length of stay or the need for additional bronchodilator treatment, and it is not recommended for routine use (Mitra *et al.*, 2004).

1.9.2: Long-Term Medical Therapy

1.9.2.1: Corticosteroids

Inhaled corticosteroids are a standard part of maintenance therapy for asthma. Studies have shown that, as a single agent, inhaled corticosteroids in a medium dosage are more effective than inhaled long-acting $beta_2$ agonists, inhaled nedocromil and leukotriene inhibitors in improving asthma symptoms and lung function in children with mild to moderate asthma (Verberne *et al.*, 1997; The Childhood Asthma Management Program Research Group, 2000; Ducharme and Di Salvio, 2004). Patients using maintenance inhaled corticosteroids found to require less use of bronchodilators and oral corticosteroids (Calpin *et al.*, 1997).

A brief, four-week study of oral montelukast added to standard dosages of inhaled budesonide in children whose asthma was not adequately controlled demonstrated improved lung function and a reduction in the number of days with asthma exacerbations (Simons *et al.*, 2001).

1.9.2.2: Leukotriene Inhibitors

The cysteinyl leukotrienes (LTC 4, LTD 4, and LTE4) are products of arachidonic acid metabolism and are released from various cells, including mast cells and eosinophils. These eicosanoids bind to cysteinyl leukotriene (CysLT) receptors. (Afridi *et al.*, 1998). The cyslt type-1 (CysLT1) receptor is found in the human airway (including airway smooth muscle cells and airway macrophages) and on other proinflammatory cells (including eosinophils). CysLTs have been correlated with the pathophysiology of asthma and allergic rhinitis. In asthma, leukotriene-mediated effects include airway edema, smooth muscle contraction, and altered cellular activity associated with the inflammatory process (Owen *et al.*, 2000).The action of Leukotrienes can be blocked through either of the two specific mechanisms:

1) Inhibition of leukotriene production.
2) Antagonism of leukotriene binding to cellular receptors.

Montelukast and Zafirlukast have been reported as leukotriene receptor antagonists of leuktriene D and E, which are components of slow reacting substance of anaphylaxis (Dockhornm *et al.*, 2000). These drugs are not indicated for acute exacerbations but are recommended for prophylaxis and chronic treatment of asthma in adults and in children.

1.9.2.2.1: Montelukast

Montelukast is a specific leukotriene receptor antagonist that has been shown to be effective in children with mild persistent asthma (Garcia *et al.*, 2005) and is recommended as a preventative agent for this group of children for the treatment of asthma (Wenzel, 1998; GINA, 2003; British Thoracic Society, 2003).

The chemical structure of montelukast is 2-[1-[[(1R)-1-[3-[(E)-2-(7-chloroquinolin-2-yl)ethenyl] phenyl]-3-[2-(2-hydroxypropaphenyl]propyl]sulfanylmethyl]cyclopropyl]acetic acid (Figure 1-3). The molecular formula of montelukast is $C_{35}H_{35}$ $ClNNaO_3$ S and the molecular weight 608.17 (Patil *et al*., 2009).

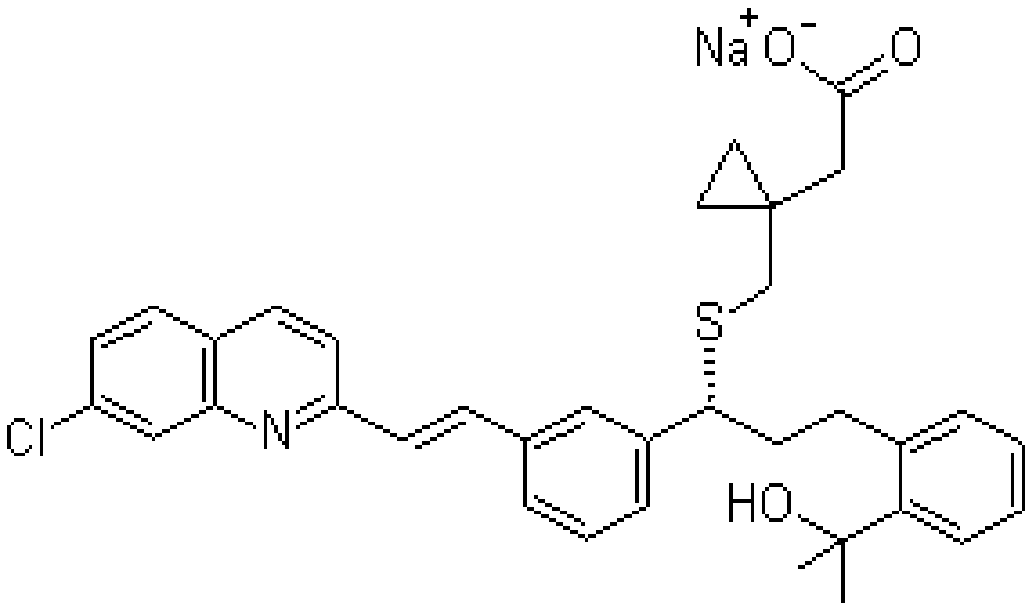

Figure 1-3 : The molecular structure of montelukast.

Mechanism of action of montelukast

Montelukast binds with high affinity and selectivity to the cyslt1 receptor (Aharony, 1998). Montelukast inhibits physiologic actions of LTD 4 at the cyslt 1 receptor without any agonist activity (Anon, 1998; Horwitz *et al*., 1998). This results in a reduction in bronchoconstriction, mucous secretion, vascular permeability and eosinophils recruitment. It also inhibits both early and late stage bronchoconstriction, implying both an anti-inflammatory and bronchodilatory action (Anon, 1999).

Pharmacokinetics of Montelukast

Absorption

Montelukast is rapidly absorbed following oral administration. After administration of the 10-mg film-coated tablet to fasted adults, the mean peak montelukast plasma concentration (Cmax) is achieved in 3 to 4 hours (Tmax) & achieved at 2 hours after fasted administration of the 4mg chewable tablet to 2 to 5 year olds [Singulair, 2001]. The mean oral bioavailability is 64%. The C_{max} found not be influenced by a standard meal in the morning (Cheng *et al*., 1996).

Montelukast administration once daily in the evening was based on comprehensive studies and no data indicate a greater benefit with administration in the evening as compared with dosing at any other time of day were found (Pajaron-Fernandez, 2006).

Maximal therapeutic response is achieved after the first dose & the half-life is reported between 2.7 to 7 hours (Knorr *et al*., 1999). Montelukast as 4 mg oral granule formulation found to be bioequivalent to the 4-mg chewable tablet when administered to adults in the fasted state & the co-administration of the oral granule formulation with apple sauce shown not to have a clinically significant effect on the pharmacokinetics of montelukast (Knorr *et al*., 2001).

In a study comparing the pharmacokinetics of a 4-mg dose of montelukast oral granules in patients between 6 to 24 months old to the 10- mg in adults observed that the estimated AUC ratio of pediatric to adult 10 mg film were similar (Migoya *et al*, 2004).

Studies comparing the pharmacokinetics of montelukast within gender indicated that montelukast had similar kinetics in males & females (Singulair, 2001).

Distribution

Montelukast is more than 99% bound to plasma proteins & the steady-state volume of distribution of montelukast averages 8-11 liters (Zhao *et al*., 1997). Studies in rats with radiolabelled montelukast indicate minimal distribution across the blood-brain barrier & concentrations of radiolabelled material at 24 hours post dose were minimal in all other tissues (Chiba *et al*., 1997).

Metabolism

Montelukast is extensively metabolized & studies performed in adults and children with therapeutic doses of montelukast, showed that plasma

concentrations of metabolites of montelukast were undetectable at steady state (Chiba *et al.*, 1997). In vitro studies using human liver microsomes indicate that cytochromes P450 3A4, 2A6 and 2C9 are involved in the metabolism of montelukast.

Elimination

The plasma clearance of montelukast averages 45 ml/ min in healthy adults. Following an oral dose of radiolabel led montelukast, 86% of the radioactivity was recovered in 5-day fecal collections and <0.2% was recovered in urine. Although, studies on bioavailability of oral montelukast indicated that montelukast and its metabolites are excreted almost exclusively via the bile, however, no dosage adjustment is necessary for the elderly or mild to moderate hepatic insufficiency (Balani *et al.*, 1997). In spite of unavailability of pharmacokinetic studies in patients with renal impairment & since montelukast and its metabolites are eliminated by the biliary route thus no dose adjustment is required in patients with renal impairment.

Adverse-effects

In clinical trials in children, the majority of the reported adverse effects found to be mild and included headache, ear infection, nausea, abdominal pain and pharyngitis & the incidence of these adverse effects was not higher than with placebo (Knorr *et al.*, 2000).

Other adverse-effects related to montelukast therapy are psychiatric disorders & hepatobiliary disorders (Khan and Hashmi, 2008). Montelukast has shown to cause transient elevation in ALT & AST activity (Marc *et al.*, 2004; Incecik *et al.*, 2007).

It was found, in some patients receiving oral corticosteroids and Zafirlukast that reductions in steroid dose were associated with Churg-Strauss syndrome (Knoell *et al.*, 1998) & they thought this may be due to reduced steroid dosage and not related to Zafirlukast. However, similar phenomenon has been reported with montelukast (Singulair, 2001).

Precautions

Montelukast is metabolized extensively by CYP 3A4, therefore caution should be exercised especially in children when it is administered with inducers of CYP3A4 such as phenytoin, phenobarbital and rifampicin (Singulair, 2001).

Montelukast crosses the placenta and is excreted in breast milk therefore should not be prescribed to pregnant and lactating women, due to lack of controlled trials (Van Adelsberg, 2005).

Efficacy of montelukast in the management of asthma in children there is a growing body of evidence indicating that leukotriene modulators, such as leukotriene-receptor antagonists play an important role as first-line therapy in patients with mild to severe asthma (Riccioni *et al.*, 2004; Bisgaard *et al.*, 2005; Laitinen *et al.*, 2005; Barclay, 2005).

Montelukast in mild & moderate persistent asthma compared with placebo; Several comparative studies in pediatric patients have been conducted in different age groups (Knorr *et al.*, 1998; Knorr *et al.*, 2000) & showed significant improvements in multiple parameters of asthma control with montelukast as day time & night time asthma symptoms, need for beta-agonist or oral corticosteroids; physician global evaluations and peripheral blood eosinophils (Stelmach *et al.*, 2002; Becker *et al.*, 2004).

Montelukast in viral-induced asthma; An efficacy study showed that montelukast effectively reduced viral induced asthma exacerbations in 2-5 year old patients with intermittent asthma over 12 months of treatment and also delayed the median time to first exacerbation by approximately 2 months (Bisgaard *et al.*; 2005). Montelukast granules have been evaluated in pediatric patients with asthma aged 6-24 month and 10-26 months in a randomized controlled trial & it was found to have a positive effect on lung function, airway inflammation and symptom scores in very young children with early childhood asthma (Van Adelsberg *et al.*, 2005). The study concluded that montelukast 4mg granule was well tolerated over 6 weeks of treatment in children aged between 6-24 months with asthma (Migoya *et al.*, 2004).

Montelukast in recurrent & persistent asthma; The efficacy of montelukast compared to corticosteroids has been studied in the management of recurrent and persistent asthma in children & found corticosteroid superior to Montelukast (Williams *et al.*, 2001; Karaman *et al.*, 2004; Garcia *et al.*, 2006; Harmanci, 2007).

In other randomized controlled trial comparing montelukast with inhaled fluticasone in 6-14 year old children with mild persistent asthma montelukast was comparable to fluticasone in increasing the percentage of asthma rescue free days but the secondary end points including FEV1, beta 2-agonist use, and quality of life improved significantly more in fluticasone treatment group (Garcia *et al.*, 2006). However, the acceptance, convenience and adherence of the patient and parent to the treatment were better with montelukast than ICS owing to its easy and simple oral once daily administered montelukast which was found to be advantageous over ICS. In another randomized controlled trial showed that the response of montelukast & inhaled corticosteroid vary within subjects owing to pharmacogentic factors (Szefler *et al.*, 2005).

Montelukast compared to long-acting β2-agoinst (LABA as add on therapy to inhaled corticosteroids (ICS) in adults; A study conducted among children revealed that add on therapy with montelukast plus low-dose budesonide was more effective than the addition of LABA or doubling the dose budesonide for controlling exhaled nitric oxide in

asthmatic children (Miraglia *et al.*, 2007; Khan and Hashmi, 2008).

Montelukast in excercise-induced bronchoconstriction; A study showed that following 8 weeks treatment with montelukast, asthma symptom score and FEV1 significantly improved in patients with excercised-induced bronchoconstriction. Montelukast was found to attenuate immediate and late phase response to exercise challenge in asthmatic children (Melo *et al.*, 2003; Payaron *et al.*, 2006).

Montelukast in the treatment of seasonal and perennial allergic rhinitis; it was evaluated in a number of randomized double blind trials compared to antihistamines. The effect of montelukast 10 mg was compared with loratidine, pseudoephedrine, cetrizine in children & adult patients were equivalent in the improving symptoms of rhinitis and quality of life index (Mucha *et al.*, 2006; Watanasomsiri *et al.*, 2008). However the night sleep quality montelukast was significantly superior to cetrizine (Chen *et al.*, 2006).

Montelukast in aspirin-induced asthma; the cysteinyl leukotrienes are the leading mediators of the airway reaction that occurs in persons with aspirin-sensitive asthma after exposure to aspirin (O'Byrne *et al.*, 1997). Leukotriene receptor antagonist found to be able to prevent this reaction (Drazen and Austen, 1999) and is considered the treatment of choice for these patients (Wenzel *et al.*, 1998; Mehta, 2000).

Other uses of montelukast

Apart from asthma other coming up roles for montelukast include chronic urticaria (Sanada, 2005) cystic fibrosis (Stelmach *et al.*, 2004), migraine (Brandes *et al.*, 2004), eosinophilic gastroenteritis (Quack, 2005), vernal keratoconjuctivitis (Lambiase, 2003), antitussive effects in cough variant asthma (Toshiyuki *et al.*, 2010) and in atopic dermatitis (Mohammad *et al.*, 2008).

1.9.2.2.2: Ketotifen

Ketotifen has the properties of the anti¬histamines in addition to a stabilizing action on mast cells analogous to that of sodium cromoglycate. It is given orally as prophylactic management of asthma, and also used in the treatment of allergic conditions such as rhinitis and conjunctivitis. Ketotifen is taken orally in dose equivalent to 1mg of Ketotifen twice a daily with food (Parafitt, 1999).

Chemical structure of ketotifen is 4-(1-Methyl-4-piperidylidene)-4H-benzo [4, 5] cyclohepta [1,2-b]thiophen-10(9H)-one hydrogen fumarate with molecular formula of C19H19NOS.C4H4O4; C23H23NO5S shown in figure 1-4(Govil and Misra, 1992).

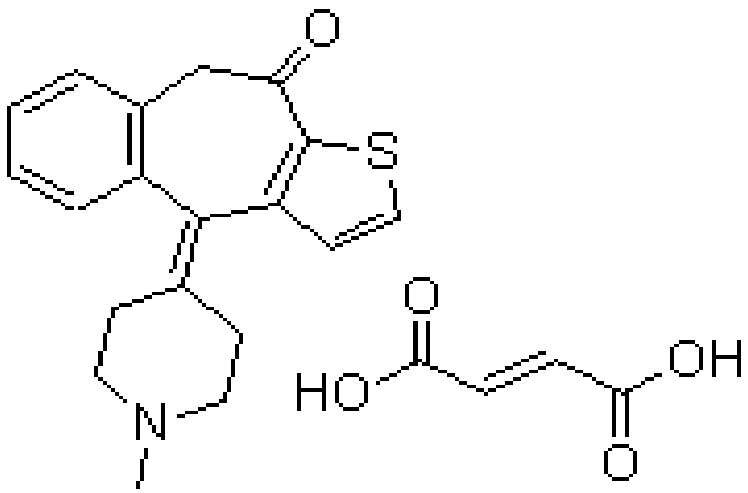

Figure 1-4 : The molecular structure of ketotifen.

Mechanism of action

Ketotifen is a relatively selective, non-competitive histamine antagonist (H1-receptor) and mast cell stabilizer. Ketotifen inhibits the release of mediators from mast cells involved in hypersensitivity reactions. Decreased chemotaxis and activation of eosinophils has also been demonstrated. Ketotifen also inhibits cAMP phosphodiesterase (Castillo *et al.*, 1991). Properties of ketotifen which may contribute to its antiallergic activity and its ability to affect the underlying pathology of asthma include inhibition of the development of airway hyper-reactivity associated with activation of platelets by PAF (Platelet Activating Factor), inhibition of PAF-induced accumulation of eosinophils

and platelets in the airways, suppression of the priming of eosinophils by human recombinant cytokines and antagonism of bronchoconstriction due to leukotrienes. Ketotifen inhibits of the release allergic mediators such as histamine, leukotrienes C4 and D4 (SRS-A) and PAF (Morita *et al.*, 1990; Schoch, 2003).

Pharmacokinetic of ketotifen

Absorption

Following oral administration absorption is at least 60%. The rate of absorption is rapid with an absorption half-life of 1 hour. Bioavailability is about 50% due to a large first pass effect (Ketotifen, 2000).

The rate absorption of two formulation syrup and oral tablet study showed a significantly more rapid rate of absorption as assessed by Tmax than oral tablet and no significant differences were observed in the extent of absorption between dosages forms (Grahnén, 1992). Bioavailability is not affected by the intake of food (Yagi *et al.*, 2002).

Metabolism and Elimination

Ketotifen is extensively metabolized to the inactive ketotifen-N-glucuronide and the pharmacologically active nor-ketotifen. Clearance of the drug from plasma is biphasic, with a half-life of distribution of 3 hours and a half-life of elimination of 22 hours in adults. Children exhibit a similar pattern of elimination. The pattern of metabolism in children is the same as in adults, but the clearance is higher in children. Children over the age of 3 years therefore require the same daily dosage regimen as adults. In infants aged less than 3 years, however, the dosage must be adjusted, since the mean levels of the drug in infants are higher than those found in children, when the same dose is given. Children have a faster clearance of ketotifen than adults and would therefore require a higher dose per kilogram body weight to give comparable steady-state levels (McFadyen *et al.*, 1997).

Precautions

Ketotifen may cause in some people drowsy, dizzy but usually disappear spontaneously with continued medication or less alert than they are normally, excited, irritable, or nervous or to have trouble in sleeping. These are symptoms of central nervous system stimulation and are especially likely to occur in children.

For patients with diabetes, the syrup form of this medicine may affect blood sugar levels. As ketotifen may lower the seizure threshold it should be used with caution in patients with a history of epilepsy.

Efficacy of ketotifen in treatment of asthma in children In a randomized placebo-controlled trial, ketotifen has been studied in mild-to-moderate asthma. Various trials showed benefit from 10 to 12 weeks of therapy when Ketotifen was given twice a day & significant improvement in PEFR, FEV_1 parameters was observed after 14 weeks of therapy (Kabra *et al.*, 2000; John and Sons, 2004).

In a double-blind crossover trial, ketotifen given to a group of young asthmatic children, no useful prophylaxis against bronchoconstriction was shown (Groggins *et al*, 1981; Shakya *et al*, 2003) & compared to disodium cromoglycate, there was a significant improvement in morning PEFR on disodium cromoglycate compared with placebo whereas ketotifen (1 mg b.d.) did not (Monie *et al.*, 1982; Croce *et al.*, 1995).

Asthmatic children receiving ketotifen were more likely to reduce concomitant medications and had significant improvement over time in asthma scores and mean flows at 75%, 50%, and 25% of vital capacity. They also had a significantly increased incidence of dry mouth and significant weight gain compared to those receiving placebo (Simons *et al.*, 2001).

In pollen-induced asthma and rhino conjunctivitis, ketotifen appeared to have good protective properties (Broberger *et al.*, 1985).In perennial rhinitis & idiopathic anaphylaxis in children, Ketotifen was shown to be effective (Fokkens and Scadding, 2004; Ditto *et al.*, 1997).For the temporary prevention of ocular itching due to allergic conjunctivitis and nasal allergic rhino conjunctivitis, ketotifen showed good efficacy (Crampton, 2003) & useful also in the management of HIV-associated malnutrition (Ockenga, 1996).

III. Materials & Methods

2.1: Equipments and Reagents

2.1.1: Equipments

Name of instruments	company	country
Minispirometer	Piko	Sweden
Spirometry	Descom – 14(Marubeni)	Japan
Centrifuge	H-19F Kokusan	Japan
Centrifuge	Hitachi	Japan
Microscope	Nikon eclipse 50 i	Japan
Minividus	Biomerieux	France
Flexor	Vita lab Scientific	Netherlands
Micropipette	Brand	Germany
Blood analyzer	Sysmex kx-21N	Japan

2.1.2: Reagents & Kits

Name of kits & reagent	company	country
Vidus Total IgE	Biomerieux	France
ALP	Vital scientific	Netherlands
ALT	Vital scientific	Netherlands
AST	Vital scientific	Netherlands
Absolute methanol	BDH	England
Leishman powder 0.15%	BDH	England
buffer solution	BDH	England

2.2: Patients & Sample collection

2.2.1: Patients

This prospective study was carried out in Kirkuk governorate between the first of November 2009 to the end of May 2010. One hundred & twenty six patients were participated in the study but 24 of them were quit from the study & only 102 patients continued the whole study period upon circumstances of responses to the drugs used in the study that are outlined in details in chapter discussion (four). The children involved in this study were from out patient's clinic, and included both sexes whom age ranged between 2 - 12 years. Asthma in the children was diagnosed by pediatricians & according to the American Thoracic Society (ATS) guidelines. The hundred and two children whom diagnosed to have mild persistent asthma on the basis of history, lung function test & physical examination were involved in the study that lasted 16 weeks according to the following parameters.

1- Patients having airflow limitation and persistent respiratory symptoms such as wheezing, chest tightness, shortness of breath and coughing particularly at night or in the early morning. These with daytime symptoms represented more than 2 days per week, but less than 1 time per day and night time symptoms represented more than 2 nights per month (Table 1-2).
2- Patients who demonstrated FEV1>80%.

Parents of the children were informed about the aim of the study, medications used, planning of treatment strategy including dose, timing, duration of treatment & the parameters that will be taken to assess the efficacy & safety of the treatment. Each child parent is asked to visit the hospital with their child at monthly interval which was considered as visits (first, second, third and fourth). Also they are instructed not to use any medication of asthma before informing us, other than β_2-agonist (salbutamol) in case they have attacked of acute bronchoconstriction.

2.2.2: Questionnaire

A structured questionnaire containing information about case history of each child was prepared for each child to be enrolled in the study (Appendix 2-1).

2.2.3: Allocation of study patients

The 102 patients whom were diagnosed as having mild persistent asthma were randomly allocated to receive medications under clinical evaluation for 16 weeks as follows:

Group I: patients who received Montelukast: included 40 patients received montelukast orally; each night for a period of sixteen weeks. For those children aged 2-5 years, 4mg granules in the evening was given and for those children aged 6-12 years, 5mg chewable tablet in the evening was given. The chewable tablets or granule are instructed to be taken after evening meal at regular interval (mostly at 9 p.m.). Chewable tablet is instructed to be taken directly with adequate water. Granules instructed to be taken either directly in the mouth, or mixed with a spoonful of cold or room temperature soft food. The parents were instructed to give the full dose within 15 minutes after opening the drug sachet for 16 weeks, during this period a patient instructed to take β2- agonist when wheezing attack occur.

Group II: patients who received Ketotifen oral syrup included 36 patients as oral syrup. One milligram every night at regular interval (at 9 p.m.) throughout period of 16 weeks, during this period a patient instructed to take β_2- agonist when wheezing attack occurs.

Group III: control group included 26 patients whom (neither received montelukast nor ketotifen medication) but they were instructed to have only β_2-adrenergic agonists during wheezing attack throughout period of 16 weeks at which the study was conducted.

Follow up chart was prepared for each child enrolled in the study. This chart contains detailed information about observations of child asthmatic symptoms or adverse-effects seen during time of study (Appendix 2-2).

2.2.4: Inclusion criteria

The inclusion criteria of patients selection was based on clinical history that included:

- Asthmatic children between ages of 2 years to 12 years.
- Patient's responses to nebulizer beta-agonist.
- Presence of persistent wheezing, chest tightness and persistent cough at night and/or early morning (mild persistent asthma). These symptoms were confirmed by physical examination and spirometry (FEV1>80% and FVC ratio).

2.2.5: Exclusive criteria

The exclusion criteria included, children:

- Patients under age of 2 years and more than 12 years.
- Presence with persistent moderate and sever of (FEV1 <80%).
- Patient with intermittent, moderate and sever symptoms of asthma.
- Patient with upper respiratory tract infections within three weeks that requires antibiotic therapy.
- Children not responded to β- agonist.
- Presence of hepatic or renal disorder.
- Previous or family history of sensitivity to montelukast and ketotifen.
- Respiratory tract, cardiac and other disorders.
- Patients who received drugs that include one or more of the following:

1- Beta -agonists (oral or long-acting or anticholinergics) within 1 week.
2- Corticosteroids within 1 month.
3- Clarithromycin, erythromycin or azithromycin within 1 month.
4- Chlorpheniramine, diphenhydramine, within 2 weeks.

2.3: Evaluation of treatment: included

2.3.1: Clinical evaluations

In this study, the clinical evaluation of lung function test included: the forced expiratory volume in one second (FEV1) & forced vital capacity (FVC) which were measured before starting medication & at each visit after treatment (at monthly interval) by minisirometry & spirometry.

Spirometry was performed in the hospital. Each child underwent measurement of FEV1 & FVC by minispirometry for those children under 6 years and chest operator (spirometry) for those children 6 – 12 years. The FVC and FEV1 values were recorded before and then every 4 week interval throughout the sixteen weeks of the treatment protocol for each child participated in the study.

The process of measurement of FEV1 & FVC by

A- Minispirometry was performed as following:
1- Quietness and relaxation were given to the child in order to get corrected measurement.
2- The child was educated how to use minispirometry and how it will aid in the treatment of the asthma.
3- After the nose of the child was closed by a clamp, he asked to take a deep breath, then expire the whole air into the instrument & then FEV1 & FVC was measured.

B- Chest operator – Function (spirometry):
1- The weight of child was measured by electronic scale and recorded.
2- The height of child was measured by stadiometer and recorded.
3- For each patient, the following data [date, sex (male= 1; female=0), age, height, weight] were registered.
4- The spacer was cleaned before and after each examination by odorless antiseptic.

5- The nose of child was closed by clamp and asked to take deep breath, & then expired the whole air volume into the instrument & the reading of FEV1 & FVC were recorded.

2.3.2: Asthma symptoms

Asthma symptoms included no. attack of wheezing, cough frequency and reduction sleep disturbance per week as outlined in Appendix 2 -2.

2.3.3: Determination of esionophils percentage and Serum Immuneglobulin E (IgE)

Blood samples (4-5ml) were obtained from each patient before drug administration & every 4 weeks after drug administration in the treatment groups (montelukast &ketotifen) & at similar times for control group.

For hematological analysis: 1 ml of the collected blood samples was introduced into tube containing EDTA anticoagulant & immediately used for preparation of blood smear for eosinophil percentage.

2.3.3.1: Estimation of esionophil percentage

Immediately after obtaining blood samples from the patient, a thin layer of blood smear was prepared & stained as follows:

1- The slide was left for at least 30 seconds in absolute methanol.
2- The stain (Leishmen stain) was drained onto the slides & left for 2 minutes.
3- A aliquot of the buffer solution was added onto the slides & then gently mixed with the stain without touching the surface of the blood film on the slide.
4- The slides were left for 3 min then rinsed with distilled water for 30 seconds & then dried.
5- Then, the slides were examined under oil immersion microscopically.

2.3.3.2: Determination of Serum IgE

Procedure

1. The required reagents removed from the refrigerator and allow them to come to room temperature for at least 30 minutes.
2. One "IgE" strip and one "IgE" SPR used for each sample, control or calibrator to be tested.
3. The selected "IgE" test code was specified & identified by "S1", and tested in duplicate.
4. Each sample was then centrifuged.
5. The calibrator, control & samples were mixed by a vortex to improve result reproducibility.
6. 100 µL of calibrator, sample or control was drawn by pipette into the sample well.
7. The SPRs and strips inserted into the instrument. The color labels would be checked with assay code on the SPRs and the reagent strips match.
8. The assay was initiated as directed in the operator manual. All assay steps were performed automatically by the instrument. Wait 30 minutes for completed of assay.
9. After assay is completed, the result of samples were read and recorded and then the SPRs and strips from instrument were removed.

2.3.4: Measurements of weight to age percentile

Weight to age percentile was estimated of each asthmatic child before starting treatment & thereafter at each visit corresponding to other parameters of drug evaluations taken in the study.

2.3.5: Effect of different treatment on liver function enzymes

From the 5ml blood samples taken, 3-4 ml of the remaining was left to clot at room temperature for 10-15mint then put it in centrifuged at 3000 rpm for three minutes. The separated serum by pipette and divided into two part, one part put in special tube of (Flexor instrument) used for the determination of liver enzymes test as serum alkaline phosphatase, serum aspartate aminotransferase (AST), serum alanine transaminase(ALT), and other part for serum IgE. These measurements were performed by using commercially available kits and manual measurement performed before treatment as a baseline and after each visit of treatment (Henderson *et al.*, 2000; Scherwin, 2003).

2.3.5.1: Determination of Alkaline Phosphatase:

Procedure: the following procedure was held at 37˚ C using wave length 405 nm.

Read against reagent blank.

1- Reagent 1(200 µL) and 10 µl of sample was mixed, then wait for 43 sec.
2- 50 µl of reagent 2 was added to the previous tube and mix, waited 4 min 43 seconds.
3- Then added 50 µL of reagent R2.
4- Mixed, and after 50 seconds incubation, the variation of absorbance per mint(A/mint) measured during 133 seconds.

Calculation

At 405 nm, with a 1 cm light path cuvette:
Activity (U\L) = A/min * 1 402

2.4.2.2: Determination of Alanine transaminase (ALT) or (GPT)

Procedure: the following procedure was held at 37˚ C using wave length 340 nm. Read against reagent blank.

1- Reagent 1(240 µL) and 30 µl of sample was mixed, then wait for 4mint and 43 sec.
2- 60 µl of reagent R2 was added to the previous tube and mix, waited 4 min 43 seconds.
3- Mixed, and after 50 seconds incubation, the variation of absorbance per mint (A/min) measured during 159 seconds.

Calculation

At 340 nm for a 1 cm path light cuvette:
Activity (U/L) = - 1746 * A\min

2.3.5.2: Determination of aspartate aminotransferase (AST) or (GOT)

Procedure: the following procedure was held at 37˚ C using wave length 340 nm.

Read against reagent blank.

1- Reagent 1(240 µL) and 30 µl of sample was mixed, then wait for 4mint and 43 sec.
2- 60 µl of reagent R2 was added to the previous tube and mix, waited 4 min 43 seconds.
3- Mixed, and after 50 seconds incubation, the variation of absorbance per mint(A/min) measured during 159 seconds.

Calculation

At 340 nm for a 1cm path light cuvette:
Activity (U\L) = - 1746 * A\min

2.3.6: Adverse experiences

At each visit parents were asked about any adverse experienced after using each medication. These experiences were recorded on the diary chart.

2.4: Statistical analysis

Data were analyzed using the statistically package social sciences (SPSS) version 16.0. Paired sample t-test was used to compare between mean values of parameters (FEV1, FVC, asthma symptoms, eosinophils percentage, serum IgE, weight to age percentile, serum ALP, serum ALT and serum AST after different time. Analysis of variance (ANOVA) was used for comparing the mean of different parameters used for evaluation of treatments between the treated groups. Chi square t -test was used for categorical variance in this study. *P value* < 0.05 was considered statistically significant.

IV. Results

One hundred and two patients involved in the study were those who reported enough symptoms to fulfill the criteria of mild persistent asthma that included, number of attack wheezing, coughing, sleeping disturbances per week & their predicted FEV1 was >80% (Table1-2). The distribution of children under study to the treatment groups are shown in (Figure 3-1).

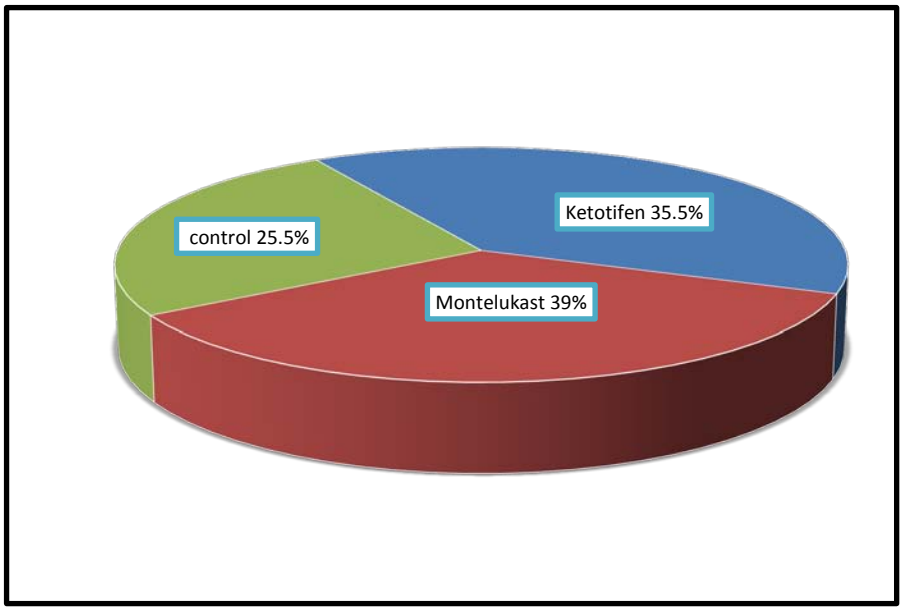

Figure 3-1 : Distributions of asthmatic children in the treatment groups.

3.1: Distribution of asthmatic children within different treatment groups

Among the 102 asthmatic children participated this study, the distribution of asthma within boys & girls were 60.8% and 39.2% respectively, (Table 3-1) and this differences were significant as shown in (Figure 3-2).

Table 3-1: Demographic data (n = 102) of children among three different treatment groups.

Treatment groups	Montelukast *n* (%)	Ketotifen *n* (%)	Control *n*(%)	Total *n*(%)
Number of subjects	40 (39.2)	36 (35.3)	26 (25.5)	102(100)
Gender				
Male	23(22.55)	21(20.6)	18(17.65)	62(60.8) **a**
Female	17(16.7)	15(14.7)	8(7.8)	40(39.2) **b**
Age				
2 -5.12 yrs	20(19.6)	20(19.6)	14(13.73)	54(52.94) **a**
6-12 yrs	20(19.6)	16(15.69)	12(11.76)	48(47.06) **a**
Mean ±SD of total age of patients	6.04 ±3.2	5.25±2.4	6.33±2.67	5.83±2.99

- Different letters means significant differences (P<0.05) between two variables.
- Same letters means that no significant differences (P>0.05) between two variables.

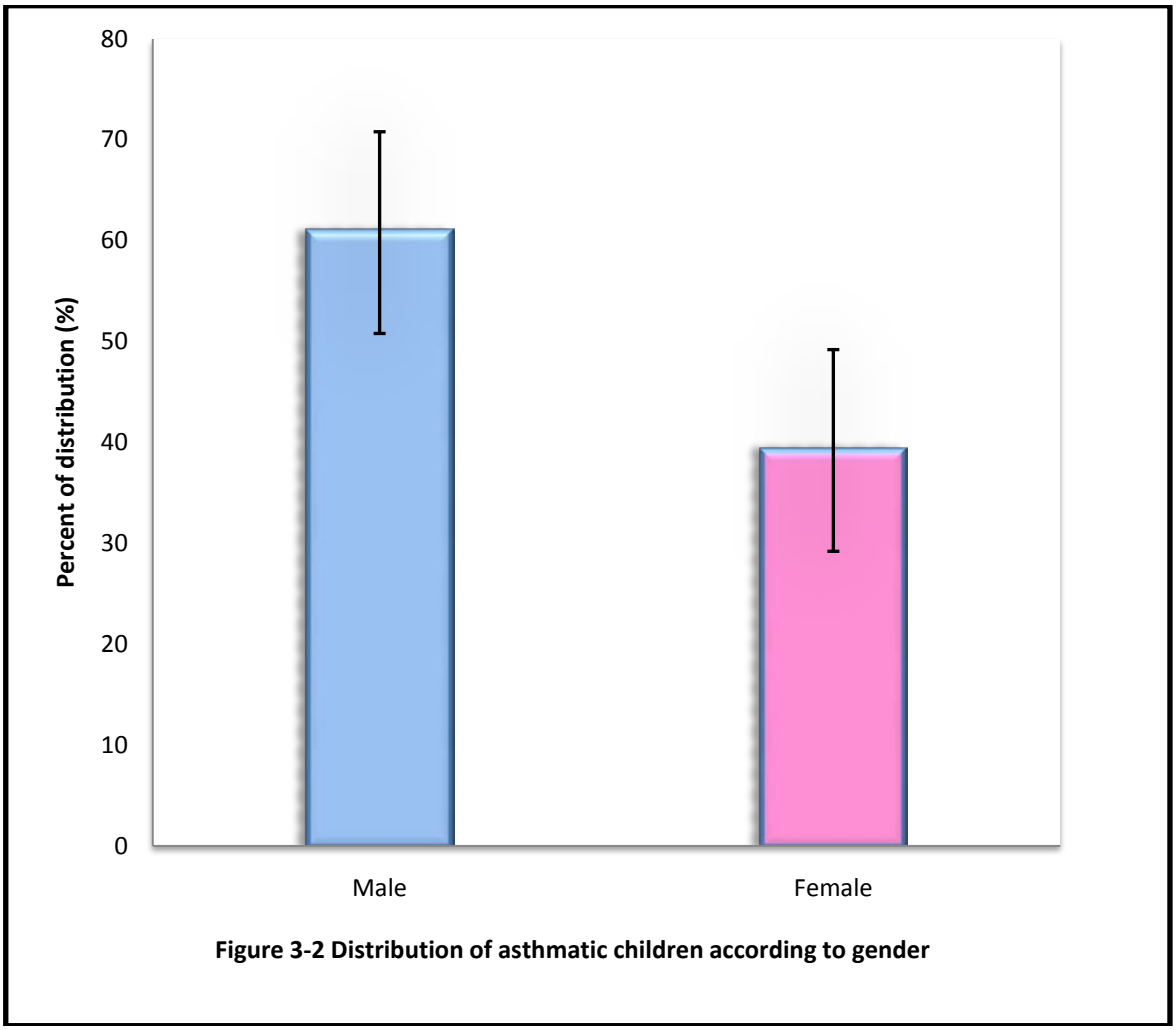

Figure 3-2 Distribution of asthmatic children according to gender

3.2: Distribution of asthma within age groups

In this study, two age groups were distributed notably 2 -5.12 years & 6-12 years old children (Table 3-1). The mean ±SD of age of participated children were (6.04 ±3.2), (5.25±2.4) and (6.33±2.67) years old in montelukast, ketotifen & control group respectively. The distribution of asthma in children within two age groups showed that the asthma distribution were 52.94% in preschool children at 2-5.12 years of age & 47.06% in school children aged 6-12 years (Figure 3-3). No significant differences were found between these 2 age groups (Table 3-1).

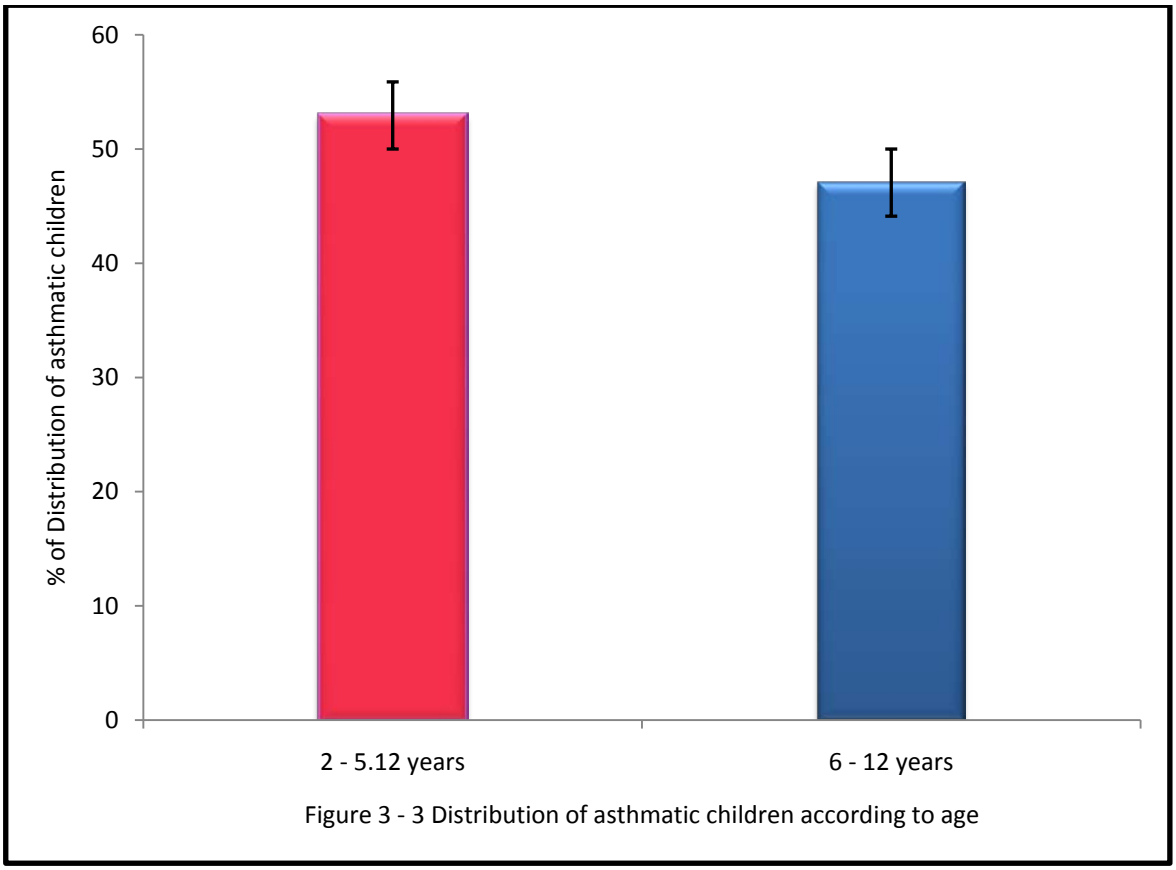

Figure 3 - 3 Distribution of asthmatic children according to age

3.3: Relation of patient's history with asthma distribution

The table (3-2) shows that within 102 asthmatic children involved in the study, children with positive history of allergic rhinitis & atopic dermatitis constituted 74.50% and 15.70% respectively and 9.8% of them had a history of both allergic rhinitis and atopic dermatitis, these differences are significantly between positive and negative allergy.

Table 3-2 : Relation of history of allergic rhinitis and atopic dermatitis to asthma distribution in the asthmatic children.

Allergy	Positive *n* (%)	Negative *n* (%)
Child with history of allergic rhinitis	76 (74.50)	26 (25.50)
Child with history of atopic dermatitis	16 (15.70)	86 (84.30)
Child with history of allergic rhinitis and atopic dermatitis	10(9.8)	-

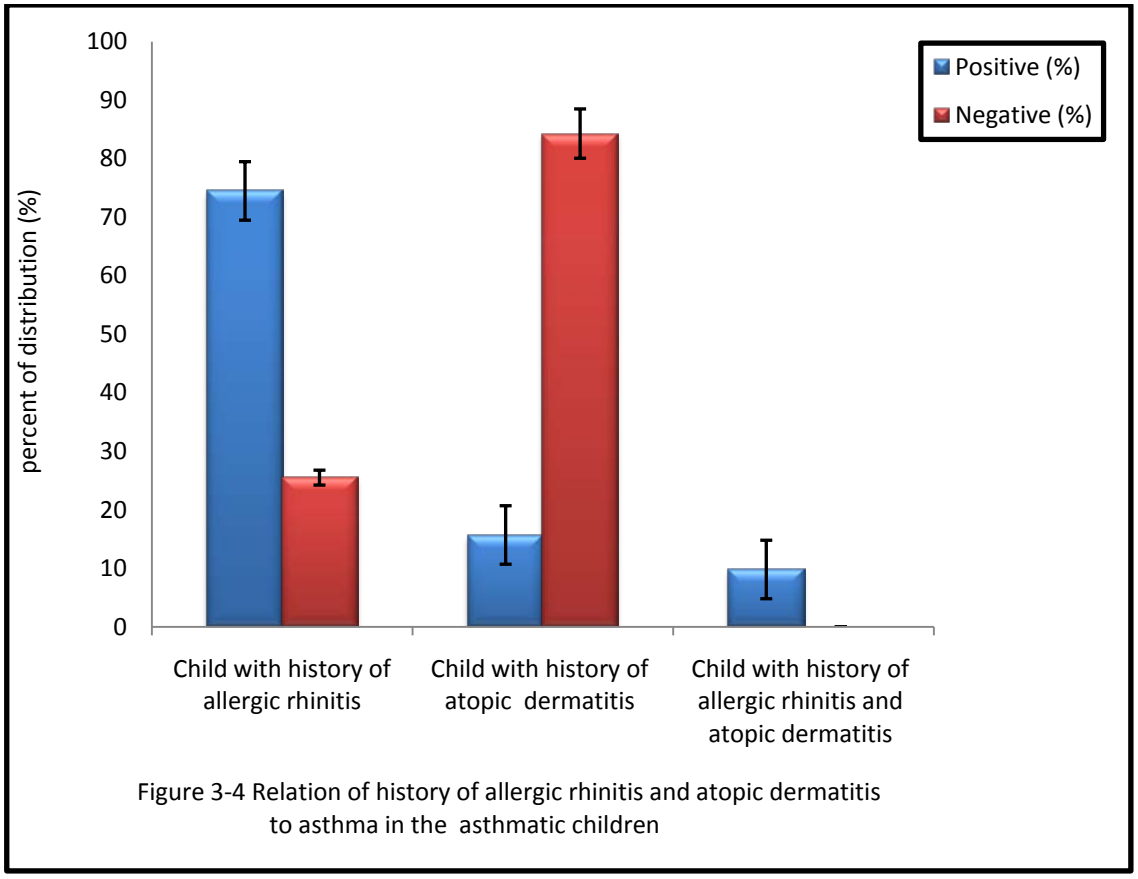

Figure 3-4 Relation of history of allergic rhinitis and atopic dermatitis to asthma in the asthmatic children

3.4: Relation of parent's history of asthma and allergic rhinitis to asthma distribution in the children.

Parent's history of allergic rhinitis & asthma constituted 96% to the distribution of asthma in the studied children, (Table 3-3). Among this percentage, mother's & fathers history of asthma & allergic rhinitis contributed to 68% and 28% respectively to the distribution of asthma within the asthmatic children.

Parent's history of allergic rhinitis found to be associated more 74% with asthma distribution in the studied children than the parent's history of asthma 22% and that the relation of maternal history of allergic rhinitis was more 56% connected with asthma distribution in the children than their paternal history of allergic rhinitis 18% as shown in (Figure 3-4). There is significant deference between the role of allergic rhinitis and asthma in parents.

Table 3-3 : Relation of parental history with asthma development in children.

Parent History	With asthma (%)	With allergic rhinitis (%)	Total (%)
Child with maternal history	12	56	68
Child with paternal history	10	18	28
No any family history	0	0	6

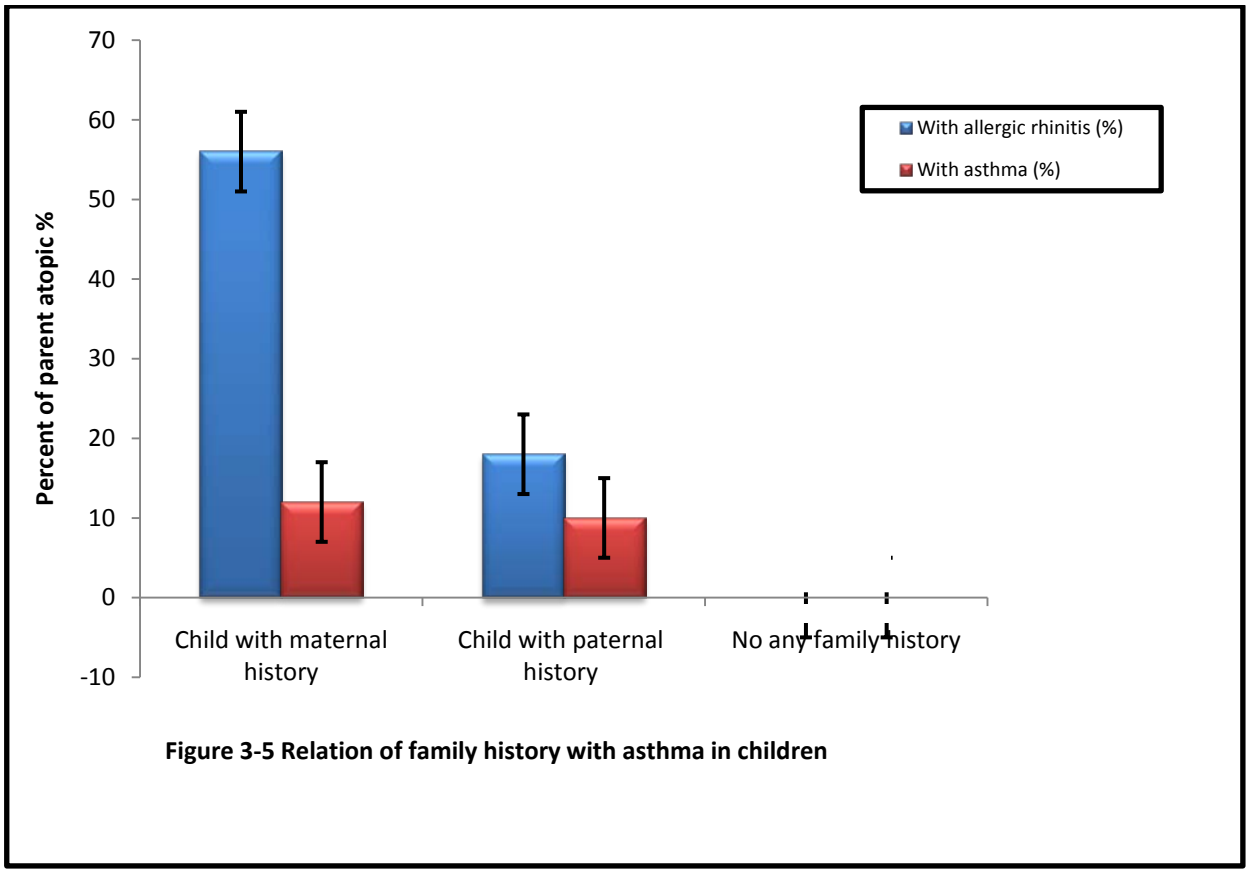

Figure 3-5 Relation of family history with asthma in children

3.5: Effect of montelukast on pulmonary function tests

Montelukast produced significant improvement in the FEV1 & FVC from the first visit of treatment to the end of the study period, when compared to the FEV1 & FVC measurement before starting treatment as shown in (Table 3-4).

Table 3-4 : Effects of montelukast on pulmonary function test (n = 40).

Pulmonary function parameters	Before treatment Mean± S.E	Visits after treatment							
		at first visit Mean± S.E	P Value	at 2nd visit Mean ±S.E	P Value	at 3rd visit Mean ±S.E	P Value	at 4th visit Mean ±S.E	P Value
FEV1 (L/Sec)	0.347 ±0.038	0.534 ±0.043	0.001 S	0.615 ±0.041	0.001 S	0.654 ±0.056	0.001 S	0.711 ±0.064	0.001 S
FVC (L)	0.479 ±0.062	0.586 ±0.093	0.001 S	0.679 ±0.107	0.001 S	0.71 ±0.112	0.001 S	0.722 ±0.114	0.001 S

Comparing the FEV1 measurement of the patients after montelukast treatment with those measurements in control group showed that improvement in FEV1 measurements started to be significant gradually started from the first visit to last visit of treatment as shown in (Table 3-5). When the effects of montelukast treatment on FEV1 measurements was compared to those in ketotifen group patients, the

improvement was not significant after the first visit of treatment but improvement became significant from the second visit to last visit of treatment.

Concerning comparison of FVC measurement of the patients after treatment with montelukast with those in control group showed significant improvement in the FVC from first visit to last visit of treatment. However, when compared the FVC value in the patients of montelukast group were compared to those patients in ketotifen group was significantly improved after the third and fourth visit (Table 3-5).

Table 3-5 : Comparison between the effects of different groups of treatment on the pulmonary function test throughout study period.

Forced Expiratory Volume per second (FEV1)											
at 1 st visit of treatment		P v alue	at 2 nd visit of treatment		P v alue	at3rd visit		P v alue	at 4 th visit of treatment		P v alue
Mo ntelukast	Ketotifen	0.264 NS	Montelukast	Ketotifen	0.005 S	Montelukast	Ketotifen	0.004 S	Montelukast	Ketotifen	0.002 S
	C ontrol	0.013 S		Control	0.005 S		Control	0.003 S		Control	0.002 S
K etotifen	control	0.414 NS	Ketotifen	control	0.553 NS	Ketotifen	control	0.058 NS	Ketotifen	control	0.052 S
F orced Vital Capacity (FVC)											
Mo ntelukast	Ketotifen	0.401 NS	Montelukast	Ketotifen	0.107 NS	Montelukast	Ketotifen	0.048 S	Montelukast	Ketotifen	0.001 S
	C ontrol	0.05 S		Control	0.024 S		Control	0.005 S		Control	0.003 S
K etotifen	control	0.112 NS	Ketotifen	control	0.739 NS	Ketotifen	control	0.459 NS	Ketotifen	control	0.309 NS

3.6: Effects of montelukast treatment on clinical symptoms of asthmatic children

Treatment once daily with montelukast produced significant improvement in asthma symptoms compared to pretreatment parameters that included attacked no. of wheezing, coughing and nocturnal awakening per week as shown in (Table 3-6). The significant reduction in number of wheezing per week was noticed from the first visit ongoing to the end of treatment period compared to those recorded before starting treatment.

A significant reduction was found in the tendency of sleeping disturbance/ week from the first visit of once daily montelukast treatment to last visit when compare to those before treatment (Table 3-6).

Coughing / week was also significantly reduced, compared to pretreatment from the first visit to last visit of treatment.

Table 3-6 : Effects of montelukast on clinical symptoms of asthmatic children (n = 40).

Clinical symptoms	Before treatment Mean ±S.E	Visits After treatment							
		at first visit Mean± S.E	P Value	at 2nd visit Mean ±S.E	P Value	at 3rd visit Mean ±S.E	P Value	at 4th visit Mean ±S.E	P Value
Wheezing	2.45 ±0.09	0.077 ±0.021	0.01 S	0.025 ±0.02	0.001 S	0.05 ±0.02	0.001 S	0±0.02	0.0001 S
Sleeping	0	1 ±0.08	0.001 S	1 ±0.07	0.001 S	1 ±0.07	0.001 S	1 ±0.076	0.0001 S

Cough	1.6 ±0.015	0.98 ±0.019	0.01 S	0.775 ±0.02 5	0.001 S	0.3 ±0.09	1E-06 S	0.25±0.06	1E-06 S

Comparison of improvement in asthma symptoms between montelukast with ketotifen treated group and control group patients, showed significant reduction in wheezing attack /week from first visit of treatment to last visit (Table 3-7). Similar significant reduction was found between montelukast group with ketotifen & control group patients in the cough attacks per week from first visit to last visit of treatment (Table 3-7). Nocturnal sleeping disturbance was reduced significant treatment when compared with ketotifen and control group as seen in the (Table 3-7).

Table 3-7 : Comparison between the effects of different groups of treatment on the clinical symptoms throughout study period.

at first visit Mean± S.E		P Value	at 2nd visit Mean ±S.E		P Value	at 3rd visit Mean ±S.E		P Value	at 4th visit Mean ±S.E		P Value
Wheezing											
Montelukast	Ketotifen	0.01 S	Montelukast	Ketotifen	0.001 S	Montelukast	Ketotifen	0.001 S	Montelukast	Ketotifen	0.001 S
	Control	0.001 S		Control	0.001 S		Control	0.001 S		Control	0.001 S
Ketotifen	control	0.284 NS	Ketotifen	control	0.095 NS	Ketotifen	control	0.004 S	Ketotifen	control	0.001 S
Cough											
Montelukast	Ketotifen	0.012 S	Montelukast	Ketotifen	0.003 S	Montelukast	Ketotifen	0.003 S	Montelukast	Ketotifen	0.001 S
	Control	0.001 S		Control	0.001 S		Control	0.001 S		Control	0.001 S
Ketotifen	control	1.02 NS	Ketotifen	control	0.309 NS	Ketotifen	control	0.185 NS	Ketotifen	control	0.01 S
Sleeping											
Montelukast	Ketotifen	0.16 NS	Montelukast	Ketotifen	0.032 S	Montelukast	Ketotifen	0.025 S	Montelukast	Ketotifen	0.012 S
	Control	0.001 S		Control	0.001 S		Control	0.001 S		Control	0.001 S
Ketotifen	control	0.327 NS	Ketotifen	control	0.018 S	Ketotifen	control	0.001 S	Ketotifen	control	0.001 S

S: significant NS: not significant

3.7: Effect of montelukast of eosinophils percentage

Significant reduction in the eosinophils percentage found from the first visit to last visit of treatment when compared to pretreatment percentage (Table 3-8).

Table 3-8 : Effects of montelukast on eosinophils percentage (n = 40).

Before treatment Mean ±S.E	Visits After treatment							
	at first visit Mean± S.E	P Value	at 2nd visit Mean ±S.E	P Value	at 3rd visit Mean ±S.E	P Value	at 4th visit Mean ±S.E	P Value
6.7 ±0.545	2.202 ±0.254	0.01 S	1.206 ±0.169	0.003 S	1.226 ±0.158	0.002 S	1.2 ±0.15	0.001 S

Comparison between eosinophils percentage in montelukast treated patients with those in control group yielded high significant differences at the first to last visits of treatment, whereas when compared with those in ketotifen group patients, showed no significant differences after the first visit of treatment but later on, of treatment (Table 3 -9).

Table 3-9 : Comparison between the effects of different groups of treatment on the eosinophils percentage throughout study period.

Eosinophils percentage											
at first visit Mean± S.E		P Value	at 2nd visit Mean ±S.E		P Value	at 3rd visit Mean ±S.E		P Value	at 4th visit Mean ±S.E		P Value
Montelukast	Ketotifen	0.066 NS	Montelukast	Ketotifen	0.01 S	Montelukast	Ketotifen	0.001 S	Montelukast	Ketotifen	0.001 S
	Control	0.002 S		Control	0.001 S		Control	0.001 S		Control	0.001 S
Ketotifen	control	0.301 NS	Ketotifen	control	0.501 NS	Ketotifen	control	0.235 NS	Ketotifen	control	0.308 NS

S: significant NS: not significant

3.8: Effects of montelukast of the serum IgE levels

Serum IgE levels were reduced significantly after treatment with montelukast from the first visit & ongoing to the last visit of once daily montelukast treatment when compared to pretreatment (Table 3-10).

Table 3-10 : Effect of montelukast on level serum IgE (IU/ml) n = 40.

Before treatment Mean ±S.E	Visits after treatment							
	at first visit Mean± S.E	P Value	at 2nd visit Mean ±S.E	P Value	at 3rd visit Mean ±S.E	P Value	at 4th visit Mean ±S.E	P Value

729.2 ±56.5	632.6 ±52.91	0.001 S	566.7 ±44.39	0.0001 S	522.1±43.32	0.0001 S	261±41.27	1E-06 S

Although no significant difference were found between the IgE levels in serum of patients in both montelukast & ketotifen treated for three visits of treatment but the differences became significantly reduced at the 4th visit of treatment in favor of montelukast group patients (Table 3-11).

Table 3-11 : Comparison between the effects of montelukast and ketotifen on the serum IgE throughout study period.

Serum IgE (IU/ml)											
at first visit Mean± S.E		P Value	at 2nd visit Mean ±S.E		P Value	at 3rd visit Mean ±S.E		P Value	at 4th visit Mean ±S.E		P Value
Montelukast	Ketotifen	0.669 NS	Montelukast	Ketotifen	0.201 NS	Montelukast	Ketotifen	0.148 NS	Montelukast	Ketotifen	0.014 S

3.9: Effect of montelukast on serum liver enzymes

3.9.1: Effect of montelukast on alkaline phosphatase (ALP) activity

Once daily treatment of patients with montelukast resulted in significant elevation in ALP activity from first visits to last visit of treatment compared to pretreatment activity (Table 3-12).

However when the activities of ALP in montelukast group patients was compared to those in control group, no significant elevation was found after the first & second visit of treatment but the elevation became significant after the third & the fourth visit of treatment (Table 3-13), whereas no significant elevation was found between the activity of ALP in patients treated with montelukast compared to those in ketotifen treated patients (Table 3-13).

3.9.2: Effect of montelukast on the activity of Alanine transaminase(ALT)

No significant differences in the serum activity of ALT was found in the patients after the first and second visit of montelukast treatment when compared with those before treatment, whereas a significant reduction in serum activity of ALT appeared after the third and fourth visit after montelukast treatment (Table 3-12).

When ALT activity was compared between montelukast treated patients with those in ketotifen & control group patients, there were no significant difference with each of the two groups until the fourth visit were a significant difference was found when compared with ketotifen & control group (Table 3-13).

3.9.3: Effect of montelukast on the activity of serum Aspartate aminotransferase (AST)

Montelukast once daily treatment produced highly significant elevation in AST activity, compared to those pretreatment values starting from the first visit to the last visit after treatment (Table 3-12).

When the activity of serum AST in montelukast-treated patients was compared to those in ketotifen & control patients, there were no significant differences between the activity of AST in montelukast-treated patients with those in the ketotifen-treated & control group patients (Table 3-13).

Table 3-12 : The effects of montelukast on serum Liver enzymes activity (n = 40).

Serum liver enzymes (U/L)	Before treatment Mean ±S.E	Visits after treatment							
		at first visit Mean± S.E	P value	at 2nd visit Mean± S.E	P value	at 3rd visit Mean± S.E	P value	at 4th visit Mean± S.E	P value

ALP	402.6 ±22.8	420.5 ±29.48	0.01 S	447.7±33.26	0.001 S	456.4 ±35.65	0.0001 S	461.7 ±37.6	0.00001 S
ALT	31 ±1.45	30.5 ±1.85	0.796 NS	29.65 ±2.11	0.776 NS	27.63 ±2.3	0.038 S	26.3 ±2.51	0.038 S
AST	11.71 ±0.59	12.1 ±0.704	0.001 S	12.4 ±1.07	0.028 S	12.31 ±1.07	0.02 S	12.1 ±1.071	0.012 S

Table 3-13 : Comparison between the effects of different groups of treatment on the serum liver enzymes throughout study period.

Serum alkaline phosphatase											
at first visit Mean± S.E		P value	at 2nd visit Mean± S.E		P value	at 3rd visit Mean± S.E		P value	at 4th visit Mean± S.E		P value
Montelukast	Ketotifen	0.503 NS	Montelukast	Ketotifen	0.394 NS	Montelukas	Ketotifen	0.424 NS	Montelukast	Ketotifen	0.489 NS
	Control	0.405 NS		Control	0.157 NS		Control	0.047 S		Control	0.011 S
Ketotifen	Control	0.561 NS	Ketotifen	Control	0.354 NS	Ketotifen	Control	0.192 NS	Ketotifen	Control	0.166 NS
Serum alanine transaminase											
Montelukast	Ketotifen	0.886 NS	Montelukast	Ketotifen	0.787 NS	Montelukast	Ketotifen	0.287 NS	Montelukast	Ketotifen	0.036 S
	Control	0.394 NS		Control	0.240 NS		Control	0.148 NS		Control	0.010 S
Ketotifen	Control	0.67 NS	Ketotifen	Control	0.17 NS	Ketotifen	Control	0.084 NS	Ketotifen	Control	0.0133 S

Serum aspartate aminotransferase											
Montelukast	Ketotifen	0.426 NS	Montelukast	Ketotifen	0.273 NS	Montelukast	Ketotifen	0.258 NS	Montelukast	Ketotifen	0.234 NS
	Control	0.391 NS		Control	0.213 NS		Control	0.126 NS		Control	0.101 NS
Ketotifen	Control	0.603 NS	Ketotifen	Control	0.032 S	Ketotifen	Control	0.053 S	Ketotifen	Control	0.001 S

S S: significant NS: non significant

3.10: Effect of ketotifen on pulmonary function test

Ketotifen produced gradual significant improvement in the FEV1 value from the first visit to last visit of treatment when compared to those before treatment. While FVC measurement was not improved significantly from first and second visit of treatment when compared to those before treatment but later on, significant improvement was established at the fourth visit of treatment (Table 3-14).

Table 3-14 : Effects of ketotifen on pulmonary function test (n = 36).

pulmonary function test	Before treatment Mean ±S.E	Visits after treatment							
		at first visit Mean ±S.E	P Value	at 2nd visit Mean ±S.E	P Value	at 3rdvisit Mean ±S.E	P Value	at 4th visit Mean ±S.E	P Value
FEV1(L\sec)	0.385 ±0.023	0.422 ±0.025	0.02 S	0.436 ±0.02	0.02S S	0.456 ±0.02	0.01 S	0.482 ±0.02	0.001 S
FVC L (L)	0.427 ±0.029	0.51 ±0.035	0.292 NS	0.51 ±0.03	0.096 NS	0.57 ±0.028	0.061 NS	0.59 ±0.03	0.01 S

When the effects of ketotifen treatment on FEV1 values was compared to those in patients in control group, the improvement in FEV1 was not significant until the last visit (Table 3-5). However, the FVC values in the patients in ketotifen group were not significantly different from those in control group throughout study period. Ketotifen effects on pulmonary function tests are compared with those of montelukast in section (3.5).

3.11: Effects of ketotifen on clinical symptoms of asthmatic children

All the clinical symptoms of asthma (wheezing, sleeping disturbances and coughing) were significantly improved starting from the first visit after ketotifen treatment to the end of study period when compared to pretreatment assessments (Table 3-15). Comparison between ketotifen & montelukast effect on improvement on asthma symptoms are outlined in section (3.6).

Table 3-15 : Effects of ketotifen on clinical symptoms of asthmatic children (n = 36).

clinical symptoms	Before treatment Mean ±S.E	Visits after treatment							
		at first visit Mean ±S.E	P value	at 2nd visit Mean ±S.E	P value	at 3rd visit Mean ±S.E	P value	at 4th visit Mean ±S.E	P value
Wheezing	2.056 ±0.1	1.38 ±0.2	0.001 S	1.19 ±0.204	0.001 S	1.05 ±0.19	0.001 S	0.68 ±0.134	0.001 S
Sleeping	0.056±0.	0.18 1±0.07	0.002	3±0.0 81	0.001	0±0.07	0.001	0.51 ±	0.001
	04		S		S		S	0.074	S
Cough	2.5 ±0.16	2.1 ±0.18	0.006 S	1.4 ±0.185	0.001 S	1.5 ±0.29	0.003 S	0.81 ±0.168	0.003 S

While, when wheezing in ketotifen treated patients was compared with those in control group, no significant differences were noticed for 2 visits but thereafter, significant reduction occurred i.e. at the third & fourth visits (table 3-7).

Sleeping disturbances was not reduced significantly in the first visit after ketotifen treatment compared to control but started to reduce significantly from the second visit ongoing to the fourth visit (Table 3-7). No significant reduction in coughing was observed for 3 visits &then at last visit coughing was reduced significant (Table 3-7).

3.12: Effect of ketotifen on eosinophils percentage

Ketotifen did not produced significant reduction in the eosinophils percentage until at the four visits of treatment produced significant reduction when compared with those before treatment (Table 3-16).

Table 3-16 : Effects of ketotifen on eosinophils percentage (n = 36).

Before treatment Mean ±S.E	Visits After treatment							
	at first visit Mean ±S.E	P Value	at 2nd visit Mean ±S.E	P Value	at 3rd visit Mean ±S.E	P Value	at 4th visit Mean ±S.E	P Value
5.968 ±0.57	3.78 ± 0.48	0.335 NS	3.586 ±0.072	0.107 NS	4.342 ±0.355	0.072 NS	4.342 ±0.35	0.034 S

When the effects of ketotifen treatment on eosinophils percentage was compared to those patients in control group, no significant difference were found (Table 3-9). Comparison with montelukast is outlined in section (3.7).

3.13: Effect of ketotifen on the serum IgE levels

Ketotifen treatment caused no significant differences in serum IgE levels when compared to those before starting treatment for 3 visits & a significant reduction was observed at the fourth visit (Table 3-17). In section (3.8), a comparison between ketotifen & montelukast effects on serum IgE was illustrated.

Table 3-17 : Effects of ketotifen on the serum IgE levels throughout study period (n = 36).

Before treatment Mean ±S.E	Visits After treatment							
	at first visit Mean ±S.E	P value	at 2nd visit Mean ±S.E	P value	at 3rd visit Mean ±S.E	P value	at 4th visit Mean ±S.E	P value
602±48.9	614.5 ±63.1	0.197 NS	459.31 ±42.6	0.178 NS	520.7 ±75.1	0.064 NS	388.7 ±48.2	0.026 S

3.14: Effect of ketotifen on serum liver enzymes activity

3.14.1: Effect of ketotifen on alkaline phosphatase (ALP) activity

A gradual significant elevation in ALP activities was observed from the first visit to the end of treatment period with ketotifen when compared with those before starting treatment (Table 3-18). Whereas, when the activity of ALP in ketotifen group patients was compared to those in montelukast (section 3.9.2) & in control group patients, no significant differences was observed throughout study period (Table 3-13).

3.14.2: Effect of ketotifen on the activity of ALT

Ketotifen treatment did not produce significant differences in ALT activity when compared with those before treatment throughout the period of study (Table 3-18).Whereas, when the activity of ALT in ketotifen group patients compared to those montelukast and control groups, no significant differences were observed until at fourth visit of treatment).

3.14.3: Effect of ketotifen on the activity of AST

Treatment of patients with ketotifen did not produced significant differences in serum asparate transaminase activity throughout period of study when compared with those before treatment (Table 3-18).

Table 3-18 : Effect of ketotifen on the activity of serum liver enzymes throughout study period (n=36).

serum liver enzymes (U/l)	Before treatment Mean ±S.E	Visits After treatment							
		at first visit Mean ±S.E	P Value	at 2nd visit Mean ±S.E	P Value	at 3rd visit Mean ±S.E	P Value	at 4th visit Mean ±S.E	P Value
ALP	393.2 ± 14.99	428.1 ±22.134	0.011 S	433.1 ±21.56	0.004 S	438.7 ±19.21	0.004 S	440.2 ±20.3	0.004 S

ALT	32.83 ±2.8	32.5 ±2.48	0.359 NS	31.1 ±2.297	0.1 NS	30.86 ±2.77	0.12 NS	31.3 ±2.36	0.124 NS
AST	13.5 ±0.81	14.4 ±1.54	0.528 NS	14.5 ±1.58	0.347 NS	14.5 ±1.494	0.352 NS	14.7 ±1.57	0.845 NS

When AST activity was compared with those of control patients, a significant elevation was shown from the second visit & thereafter to the end of treatment period. The comparison with montelukast effects on AST activity were elucidated in section (3.9.3).

3.15: Pulmonary function test in control group

Table (3-19) reveals the pulmonary function tests in control group patients whom were only kept on β2 agonist intermittent treatment. No significant differences were shown in FEV1 and FVC values throughout period of study when compared with those before treatment.

Table 3-19 : Pulmonary function test in control group (n = 26).

pulmonary function test	Before treatment Mean ±S.E	Visits After treatment							
		at first visit Mean ±S.E	P Value	at 2nd visit Mean ±S.E	P Value	at 3rd visit Mean ±S.E	P Value	at 4th visit Mean ±S.E	P Value
FEV1 (L\sec)	0.41 ±0.03	0.40 ±0.039	0.354 NS	0.4 ±0.029	0.503 NS	0.41 ±0.033	0.391 NS	0.41 ±0.03	0.38 NS
FVC (L)	0.49±0.03	0.49 ±0.042	0.2 NS	0.488 ±0.03	0.184 NS	0.499 ±0.039	0.153 NS	0.52 ±0.045	0.125 NS

The comparison between pulmonary function tests (FEV1 & FVC) in montelukast or ketotifen treated patients with control group patients were clarified in sections 3.5 and 3.10 respectively.

3.16: Clinical symptoms of control patients

The episodic wheezing, cough & nocturnal sleep disturbances were not significant different throughout study period when compared with those before treatment (Table 3-20). Comparisons with montelukast & ketotifen group patients were exemplified in sections 3.6 and 3.11 respectively.

Table 3-20 : Clinical symptoms of control patients (n = 26).

Clinical symptoms	Before treatment Mean ±S.E	After treatment at first visit Mean ±S.E	P Value	at 2nd visit Mean ±S.E	P Value	at 3rd visit Mean ±S.E	P Value	at 4th visit Mean ±S.E	P Value
Wheezing	2.31 ± 0133	2 ± 0.0124	0.103 NS	2.15 ± 0.0143	0.381 NS	2.23 ± 0.0178	0.483 NS	2.36 ± 0.0152	0.574 NS
Sleeping	0 ±0	0 ±0	0.067 NS	0 ±0	0.44 NS	0.0384 ± 0.0385	0.542 NS	0.07± 0	0.635 NS
Cough	2.5± 0.169	2.5± 0.0177	0.126 NS	2.2± 0.0199	0.371 NS	2.23 ± 0.0188	0.658 NS	2.582 ± 0.0189	0.724 NS

3.17: Eosinophils percentage in control group

In (Table 3-21) eosinophils percentage were shown increased significantly starting at the second to the last visit of study period when compared with those before treatment. In sections 3.7 and 3.12, comparisons between control group & montelukast group patients were demonstrated respectively.

Table 3-21 : Eosinophils percentage in control group patients (n = 26).

Before treatment (Mean ±S.E)	After treatment at first visit Mean ±S.E	P Value	at 2nd visit Mean ±S.E	P Value	at 3rd visit Mean ±S.E	P Value	at 4th visit Mean ±S.E	P Value
5.5 ±0.496	5.56 ±0.438	0.911 NS	5.97 ±0.42	0.011 S	5.9 ±0.478	0.025 S	6.2 ±0.543	0.037 S

3.18: Liver enzymes estimation in control group

3.18.1: Serum alkaline phosphatase (ALP) activity

Estimation of activity of serum alkaline phosphatase in control patients showed no significant difference throughout period of study when compared with those before treatment (Table 3-22). The comparisons with montelukast & ketotifen group patients were outlined in sections 3.9.1 & 3.14.1 respectively.

3.18.2: Serum Alanine transaminase (ALT) activity

Significant elevation in the serum activity of ALT in control group patients were shown from the first visit to the last visit of study period when compared with those before starting treatment (Table 3-22). Sections (3.9.2) & (3.14.2) reviewed the comparison between control group patients with those of montelukast & ketotifen patients respectively.

3.18.3: Serum Aspartate aminotransferase (AST) activity

Estimation of AST activity in control patients exhibited no significant difference throughout period of study when compared with those before treatment (Table 3-22), and the comparison between control, montelukast & ketotifen group patients were elucidated in sections 3.9.3 & 3.14.3 respectively.

Table 3-22 : Serum liver enzymes estimation activities in control group (n = 26).

Liver enzymes (U\L)	Before treatment Mean ±S.E	After treatment							
		at first visit Mean ±S.E	P Value	at 2nd visit Mean ±S.E	P Value	at 3rd visit Mean ±S.E	P Value	at 4th visit Mean ±S.E	P Value
ALP	389.4 ±22.5	389.2 ±19.47	0.912 NS	390.4 ±18.7	0.863 NS	390.1 ±26.95	0.765 NS	397.2 ±23.56	0.625 NS
ALT	26.5 ±1.97	31.9 ±1.58	0.001 S	32.625 ±2.1	0.004 S	33.93 ±2.24	0.004 S	32.824 ±2.21	0.039 S
AST	10.6 ±0.66	10.12 ±0.487	0.637 NS	10.6 ±0.631	0.423 NS	9.7 ±0.541	0.457 NS	10.1 ±0.51	0.476 NS

3.19: Effect of montelukast and ketotifen on weight measurement

3.19.1: Effect of montelukast on weight-age percentiles of asthmatic children

A significant increase of weight percentile was observed after montelukast once daily treatment from the first visit and ongoing throughout the treatment period when compared with those before treatment as shown in (Table3-23).

Table 3- 23 : Relation of montelukast treatment on weight-age percentile of asthmatic children (n = 40).

weight to age percentile measurement	Before treatment (mean ± S.E.)	After treatment							
		at first visit (mean ± S.E.)	P value	at 2nd visit (mean ± S.E.)	P value	at 3rd visit (mean ± S.E.)	P value	at 4th visit (mean ± S.E.)	P value
	44.69±5.73	53.1±5.3	0.001 S	55.87±5.2	0.001 S	58.3±5.04	0.001 S	59.2±4.9	0.001 S

When the effects of montelukast treatment were compared with those of ketotifen group, no significant differences were seen throughout period of study, table 3-24. While when compared with those of control group, significant difference was found at the second visit of treatment & thereafter.

Table 3-24 : Comparison between the effects of different groups of treatment on weight-age percentile throughout study period.

Weight to age percentile											
at 1st visit		P value	at 2nd visit		P value	at 3rd visit		P value	at 4th visit		P value
Montelukast	Ketotifen	0.666 NS	Montelukast	Ketotifen	0.945 NS	Montelukast	Ketotifen	0.827 NS	Montelukast	Ketotifen	0.597 NS
	Control	0.163 NS		Control	0.046 S		Control	0.009 S		Control	0.008 S

ketotifen	control	0.189 NS	ketotifen	control	0.036 S	ketotifen	control	0.028 S	ketotifen	control	0.016 S

3.19.2: Effect of ketotifen on weight-age percentile of asthmatic children

Table (3 -25) show significant gradual increase of weight percentile starting from the first visit and to last period of study after ketotifen treatment.

Table 3- 25 : Relation of ketotifen treatment on weight-age percentile of asthmatic children(n=36).

weight to age percentile measurement	Before treatment (mean ± S.E.)	After treatment							
		at first visit (mean ± S.E.)	P value	at 2nd visit (mean ± S.E.)	P value	at 3rd visit (mean ± S.E.)	P value	at 4th visit (mean ± S.E.)	P value
	44.44±5.7	48.8±5.7	0.011 S	54.2±5.8	0.002 S	59.2±5.8	0.001 S	62.4±5.85	0.001 S

When the effects of treatment of ketotifen was compared with those of control group, no significant difference were seen at the first visit, however significant difference were started to appear from the second visit to last visit of treatment.

3.19.3: Weigh-age percentile of control group patients

Table (3-26) show that significant reduction from the first visit and ongoing throughout period of study in weight-age percentile of the asthmatic children.

Table 3-26 : Percentile measurement in control group throughout period of study (n = 26).

Percentile weight to age	Before treatment (mean ± S.E.)	After treatment							
		at first visit (mean ± S.E.)	P value	at 2nd visit (mean ± S.E.)	P value	at 3rd visit (mean ± S.E.)	P value	at 4th visit (mean ± S.E	P value
	36.34±5.9	35.5±6.1	0.001 S	34.7±5.9	0.001 S	32.6±5.7	0.001 S	32.3±7.1	0.001 S

3.20: Adverse effects of montelukast treatment on asthmatic children

Adverse effects associated with montelukast treatment are shown in (Table 3-27). These adverse-effects were observed in 25 patients out of the 40 patients enrolled in montelukast group. Agitation (28%), nasal irritation and skin rash each constituted 13% while 2.5% of them showed lip edema.

Table 3-27 : adverse effects of montelukast treatment (in 25 children) during the period of study.

Adverse Effects	Montelukast (n=40)		Disappearance of the adverse effect
	No.	%	
Agitation	11	28	Within 2 month after drug withdrawal
Nasal irritation	5	13	Within one month of drug withdrawal

Skin rash	5	13	Within one week
Increase appetite	3	8	After 2 weeks of drug discontinuation
lips edema	1	2.5	Within one month after drug withdrawal.

3.21: Adverse effects of ketotifen treatment on asthmatic children

Nasal irritation, skin rashes, increase appetite and sedation effects were shown in 32 out of 36 patients after ketotifen treatment and all were disappeared after drug discontinuation (Table 3-28).

Table 3-28 : adverse effects of ketotifen treatment (in 32 children) during the period of study.

Adverse Effects	ketotifen (n=36)		Disappearance of adverse effect
	No.	%	
Sedation	17	47	After 1 month of drug discontinuation
increase appetite	10	27.7	After 1 month of drug discontinuation
Skin rash	3	8.3	within 4 days
Nasal irritation	2	5.5	After 3 weeks of drug discontinuation

V. Discussion

The present study was designed to determine the ef¬ficacy and safety of montelukast and ketotifen as controller treatment in asthmatic children.

In the present study, the children distributed to preschool children and school children according to their age which were between 2 to 12 years and most children diagnosed with asthma according to the criteria of mild persistent asthma were preschool children (5.25±2.4 years) although no significant differences were shown between these groups which was inconsistent to those reported by (Martinez *et al.*, 1995; Castro-Rodriguez, 2000; Uyan *et al.*, 2003; Davis, 2009) as that asthma prevalence were higher in preschool children. This difference is most probably related to the small number of patients observed in this trial.

In this trial, both sexes were found affected although the distribution by sex revealed a ratio of 1.55:1 (male/female) but it is very close to those ratios (1.6:1 & 1.55:1) found in other studies (Carr *et al.*, 1992; Beasley, 2002; Alexander, 2005). The predominance of boys over girls in this study was significant and similar documentations about the predominance of male sex until adolescence over female has been reported by others as well (Martinez *et al.*, 1995, Sundell, 2006) which has been attributed to differences in the structure & function relationship of the lung & airways, where girls

have airways that are more proportionate to the size of their lungs, while the airways of boys are proportionately smaller, compared to lung size (Davis, 2009).

Extensive epidemiologic researches have established links between patient's own history of atopy to asthma (Volcheck, 2004; Jonathan and Spergel, 2010). These links were observed also in this trial as 90.2% of the children had previous history of atopy which was significant and it was distributed as 74.5% to allergic rhinitis and 15.7% to atopic dermatitis and only 9.8% had no history of both atopy and it is obvious that history of allergic rhinitis was more related to asthma distribution in the studied children than history of atopic dermatitis, a similar correlation was also reported by (Leynaert, 2000) that rhinitis constituted 10.8% to the prevalence of asthma in the studied population versus 3.6% to 5% and to other study that showed frequency of allergic rhinitis was 61.6% among individuals with asthma versus 6% among non-asthmatic (control) subjects (Alsamarai *et al*., 2009).

Basically, the factors that are associated with asthma are of two types: host factors & enviromental factors (Sunyer *et al*., 1997) so that the 9.8% of the asthmatic children in our study with no previousd history of atopy is probably related to enviromental& other factors which are numerous that tend to iniate asthma pathology& exacerbate symptoms which are important in the development, occurance, perpetution of asthma symptoms in children (Spork, 1990; Sundell, 2006).

Association between asthma & family history proposed that in families where neither parent had asthma nor allergic rhinitis, 6% of the children has asthma & that in families where one parent had asthma, 20% of the children had asthma whereas in families where both parents had asthma, 60% of the children had asthma (Hederos, 2007) and as well, in the present study we found that among the 102 asthmatic children, 96% of them, their parents had history of asthma and/or allergic rhinitis, which is also similar to those observed by (Kilpelainen *et al*., 2001), 1325 children at 7 years of age that the highest prevalence of atopic disease among children was in those with both parents had an identical type of atopic disease with 72% risk, and the lowest among children of parents without an atopic disease (10%).

Our finding of association of mother's history of atopy (68%) that was higher to asthma development in the children than father's history of atopy (26%) is found to be inconsistent with those reported in a survy of asthma prevalence among 1021 asthmatic children that 29.7% of them had mothers with history of asthma or rhinitis or allergy and 22.4% having father's with history of asthma or rhinitis or allergy (Svanes *et al*., 1999). Furthermore the history of allergic rhinitis was the most frequently reported type of parental atopy in our study which has also been reported by other's as parental history of allergic rhinitis was the strongest risk factor for asthma (Kilpelainen *et al*., 2001; Wickens *et al*., 2002; Pallasaho, 2006).

The primary efficacy endpoint taken in this trial as one of the diagnostic test for pulmonary function was the change from baseline in FEV1 & FVC values.

Highly significant improvement in FEV1 value was obtained after once daily montelukast treatment of the asthmatic children & montelukast resulted in an increase in FEV1 value from the baseline by > 50%, >70%, >80%, & >90% at the first, second, third & fourth visit after treatment respectively which means that the asthmatic children have better ability to exhale air from their lungs, although the post-treatment values still did not reach the mean FEV1 value of (mean1.11 L/sec) according to height in normal healthy child (Polgar and Weng, 1979). Similar finding was reported by (Jarvis and Markham, 2000; Meyer *et al*., 2003; Becker *et al*., 2004; Fall and Kopeć, 2010).

In spite of significant improvement in FVC value from the first visit after treatment until the end of the study period, but the percent of increase from baseline value determined was only 22%, 41%, 48% & 50% after the first, second, third & fourth visits respectively of montelukast once daily treatment although it was still less than the mean value (1.12 L)in a normal child of according to height (Polgar and Weng, 1979). This means that montelukast treatment produced better expelling in the lung's air volume in the asthmatic children & that a greater volume over the time course of the FVC test is expelled but less than it would be expelled in a normal healthy individual.

However, when we determined the FEV1/FVC ratio which represents the percent of the lung size (FVC) that can be exhaled in one second; we find that this ratio is greater than 90% from the first visit after montelukast treatment & forward. Thus it is obvious that once daily montelukast treatment for 16 weeks had resulted in a significant improvement in pulmonary function because this ratio indicate that the children can breathe out 90% of the inhaled air in the lungs in one second.

This study involved not only evaluation of improvements in lung function test (FEV1 & FVC) before & after montelukast treatment as controller therapy of mild persistent asthma in children for a period of 16 weeks but also comparing montelukast efficacy with control group & ketotifen.

The finding that once-daily treatment with montelukast as compared with control, significantly improved multiple efficacy end points (FEV1 & FVC) from the first visit & thereafter over the 16 -weeks period in the studied children indicates its high efficacy in maintaining better breathing capacity in these asthmatic children. This result is also confirmed by findings of (Noonan *et al*., 1998; Knorr et al., 2001) whom obtained 40-80% improvement in FEV1 when montelukast administered once daily for 3 weeks &of other findings.

Furthermore, our results showed the superiority of montelukast over ketotifen in improving FEV1 that started to be significantly gradually better from the second visit & thereafter ongoing to the fourth visit after treatment. This reveal the greater potency of montelukast in performing better pulmonary function in these children with mild persistent asthma and it might be explained on the fact that although both drugs exhibited anti-inflammatory effect but revealed that leukotrienes (LTC4,D4,E4) had great involvement than histamine in the pathophysiology of mild persistent asthma in children under this investigation as shown by the greater efficacy of the antileukoterine, montelukast over ketotifen as antihistaminic drug. The result of our study is corroborative with other studied (Nicosia et al., 2001; Riccioni *et al*., 2002; Capra, 2006; Capra et al., 2007; Peters-Golden and Henderson, 2007) that support the greater role of leukotrienes in mediating bronchocostriction, mucous secretion, with a subsequent reduction in airway inflammation (Harmanci, 2007).

Our finding also confirm the greater role of leukoterines over histamine in mediating asthma symptoms as administration of ketotifen for 12 weeks produced no significant improvement , compared to control, in FEV1 until 16 weeks after treatment where as FVC values did not differed significantly from those of control over the 16 weeks of once daily ketotifen treatment.

In spite of the significant improvement noticed in the FEV1 values in the asthmatic children when they are compared before & after ketotifen treatment from the first visit & onward to the end of the study period but the extend & level of significance was much less than those obtained in montelukast treated group children. Besides that the FVC values was improved only significantly from baseline values after 16 weeks of ketotifen treatment confirm the lower efficacy of ketotifen in ameliorating symptoms of asthma in children involved in the present study. Indeed the percentage change in FEV1 from baseline, was 9.6 %, 13.25%, 18.44% & 25.2% after the first, second, third & fourth visit respectively of ketotifen once daily treatment and is clearly less than those produced after montelukast treatment thus illuminating the importance of leukotriene antagonists in the treatment of asthma. Indeed, the asthmatic children that were placed on ketotifen therapy were 42 but as the study period was going on, 6 of them quit taking ketotifen & visiting the hospital for further evaluation of the therapy as they found no obvious relieve of their asthma symptoms & thus we followed up investigation only 36 patients to the end of study period & all the data that are stated in all the evaluations were those of only the 36 patients stayed to the of the trial.

Studies comparing montelukast with other antihistaminic agents as ketotifen, loratidine, fexofenadine in the treatment of asthma have outlined the benefits of anti-histaminic drug in relieving asthmatic symptoms but they also pointed out the preference of montelukast over antihistaminic agents as anti-inflammatory pharmacotherapy reversing brochoconstriction & reducing airways inflammation through their ability to reach lower airways and improves the peripheral functions thus play a crucial role in the evolution of asthma (Anon, 1999; Pajaron-Fernandez, 2006; Walia *et al*., 2006).

This predominance of montelukast over ketotifen can be explained by that leukotrienes in the airways contributes more to the physiological and pathological changes of asthma (more potent than acetylcholine and histamine as contractile agonists of human airways (Barnes *et al*., 1984; Drazen and Austen, 1999) plus that referring to earlier reports which stated that cysteinyl-leukoterines are approximately 100-10000 times as potent on molecular basis than histamine in causing constriction of the airways (Wiess, 1982; Weiss, 1983; Smith, 1985).

Patients with asthma often become wheezy at night with an overnight fall in forced expiratory flow rates (Montplaisir *et al*., 1982). They also sleep less well, become more hypoxaemic during the night, and have more irregular breathing during sleep than do healthy people of similar age (Catterall, 1983) therefore one of the aims of asthma pharmacotherapy is subjected toward relieving in both day & night asthma symptoms.

Montelukast by virtue of its anti-inflammatory, bronchodilating effects (Anon, 1999; Pajaron-Fernandez, 2006) caused significant improvement in pulmonary function that contributed very well in ameliorating asthma symptoms from which, the asthmatic children complain adding heavy burden on their health & performance by reducing their physical activity & school attendance. The significant reduction in the attack wheezing, sleep disturbance & coughing frequencies shown after montelukast once daily treatment , compared to pretreatment symptoms in this trial through the first visit to the fourth visit after treatment, indicates its powerful anti-inflammatory effect through inhibition of cysteinyl leukoterines thus reducing bronchial hyperresponsiveness, mucus secretion & inflammation of the airways since cysteinyl leukoterines have been shown to be abundant in bronchi of asthmatic patients as well as in nasal fluids of patients with allergic & seasonal rhinitis (Walker and Sheik, 2002) and their inhibition will be a key factor in relieving asthma day & night symptoms (Pullerits *et al*., 1999; Pullerits *et al*., 2002) as shown in this study.

A linear relationship was noticed between improvement in FEV1, FVC values simultaneously with the reduction in asthma symptoms, from the first visit after montelukast once daily treatment, compared to pretreatment parameters suggesting the direct relationship between improvements in pulmonary

function test & the relieve of asthma symptoms in the studied children in our trial.

As compared to control group, montelukast also showed significant higher potency in reducing wheezing, sleeping disturbances & coughing from the first visit & ongoing to the last visit suggesting an optimal asthma control is being achieved in these asthmatic children & support what has been claimed in its pharmacokinetic study that its action starts within days after treatment (Paige, 1998). Whereas salbutamol (control group) effect by activating β2- adrenoceptors and hence cause direct relaxation of bronchial smooth muscles (Stahl *et al*., 2003) was so weak that was un able to produced any significant improvement in neither pulmonary function nor in asthma symptoms throughout the study period. Honestly, the asthmatic children involved as control were 44 but as no good response they got from this β-2 agonist therefore, 18 of them gave up this medication & 26 were remained to continue this trial as a comparison group & data included in this study were of those remains 26 patients only.

Montelukast was found to be superior to ketotifen in reducing wheezing & coughing from the first to the fourth visit after treatment as there were significant reducing both of these symptoms, although reduction in sleep disturbance started to be significantly from those in ketotifen treated group after two visits & thereafter. These results demonstrate that both ketotifen & montelukast are effective in relieving asthma symptoms through their inhibition of histamine & leukotrienes inflammatory effects and since ketotifen is known to cause sedation (Shakya, 2003) & indeed sedation were experienced by children in this group, so this is more likely contributed to the reduction of sleeping disturbance that ultimately reduced coughing & wheezing.

Peripheral blood eosinophils serve as an indi¬cator of airway inflammation (Shields *et al*.; 1999). Montelukast through inhibiting cysteinyl leukoterine (specifically LTD4) binding to cystl LTs-1 receptor (Mita *et al*., 2001; Harmanci, 2007; Munoz *et al*., 1997) prevented activation of eosinophils & release of more leukotrienes & caused significant decrease in the level of eosinophils in the peripheral blood , compared to pretreatment values that was acpercentageed from 67 to 82% in eosinophils percentage at the first visit ongoing to the fourth visit respectively after montelukast daily treatment. This percentage of reduction was close to those reported by (Anon, 2003) and further supported by others (Knorr, 1998). Likewise, significant differences in eosinophils percentage were found between montelukast treated group & those of control group from the first visit ongoing to the fourth visit of treatment which also postulated that montelukast significantly reduced peripheral blood eosinophils by 4% compared to a 3.7% increase in eosinophils of the control group (Ramsay,1997; Schmitt-Grohé *et al*., 2002; Bisgaard, 2004).

The significant differences seen, in the present study, between montelukast & control group comes from the fact that eosinophils percentage was elevated in control group in contrast to those in montelukast treated group, owing to the nature of inflammatory process & severity of asthma that was not controlled by salbutamol in the control group patients besides that salbutamol lacks anti-inflammatory effects (Oriol *et al*., 2008). Although no significant differences in eosinophils percentage was obtained between montelukast & ketotifen group patients after 4 weeks of daily treatment by either drug, but the differences became significant after 8 weeks & ongoing to the 16 weeks of treatment. This, of course would be related to the insignificant reduction in eosinophils percentage throughout 12 weeks of the ketotifen once daily treatment & that the difference became only significant after 16 weeks of ketotifen treatment, compared to control group by 27.25% only.

These findings are consistent with those reported in patients with allergic rhinitis (Philip et al., 2002) who found that montelukast reduced peripheral blood eosinophils by 16.9% from control whereas loratidine (an H1 antihistamine similar to ketotifen) did not reduced eosinophils percentages.

An explanation for these differences can be related to the great accusation about the greater role of leukotrienes (Chipps, 2004) over histamine (Barnes *et al*., 1984; Drazen and Austen, 1987) to the patho-physiology of asthma that elucidated montelukast potency over ketotifen in asthma therapy. Our results coincide with other studies that clearly demonstrated that treating subjects with allergic asthma had more response to antileukoterins than to antihistamine (Wiqar *et al*., 2008).

Besides this, we notice that the studied children had previous history of allergic rhinitis & a correlation between the degree of bronchial hyper responsiveness (a cardinal feature of asthma) and peripheral blood eosinophilia has been observed in subjects who exhibited a dual response following allergen challenge (Horn *et al*., 1975) and it was clarified when allergic rhinitis is associated with bronchial asthma, the eosinophil values was increased above the normal indicating relation between asthma & allergic rhinitis (Chowdary *et al*., 2003).

Among the most sensitive and widely used liver enzymes are the aminotransferases. aspartate aminotransferase (AST or SGOT) and alanine aminotransferase (ALT or SGPT) and Alkaline phosphatase (ALP) (Nyblom et al., 2006).

Treatment with montelukast was associated by elevation in activity of ALP from the first visit & forward compared to pretreatment values. Such finding has been reported only in a case report (Incecik *et al*., 2007).The elevation of ALP seen after montelukast treatment is most probably related to a cholestatic &/or

hepatocyte injury (Sarah and Corathers 2006) and according to montelukast pharmacokinetics studies, (Paige , 1998), montelukast undergoes extensive metabolism in the liver by the cytochrome P450 enzyme system, and is almost exclusively excreted with its metabolites into the bile (Schoors et al., 1995; Cheng *et al.*, 1996; Chiba *et al.*, 1997) leading to elevated ALP activity in blood. Although we found a dramatic increase in ALP activity after montelukast treatment but these were not significantly higher than those of control group patients until after the third and fourth visit of treatment. Such results must require special attention & necessitates recommendation for ALP continuous monitoring after prolonged treatment with montelukast, although the values of ALP still are less than those expected in such age group children since up to 500 U/L are considered within normal range in these growing age children (Butch et al., 1989) but we assume that the study period was not so long for accusing such high elevation to developmental period in the children.

It seems that montelukast caused asymptomatic hepatotoxic effect although, no pathophysiologic mechanism has been proven to explain our result or the others reported with similar drugs but immunologically induced hypersensitivity reaction, hepatoto metabolites, drug reactions, or unexplained idiosyncratic responses may be involved (Reinus *et al.*, 2000; Goldstein *et al.*, 2004).

Although review of all reported cases of leukotriene modifier– induced hepatitis revealed that hepatic toxicity may develop within weeks or as late as 13 months after start of therapy. With the increasing use of these drugs, coupled with monitoring of liver function, more asymptomatic cases may become apparent. Serial liver function testing has been recommended for patients receiving zileuton (Montvale, 2002) but not for those receiving zafirlukast or montelukast (Reinus et al., 2000; Montvale, 2002). On the basis of our cases and literature review, we recommend that liver function be tested within 4 weeks of initiation of therapy with any leukotriene modifier and that testing be repeated at 3, 6, and 12 month.

Similarly, ketotifen induced gradually significant elevation in ALP activity from the first visit and onward, compared to pretreatment values which correspondence to those findings with montelukast in this study since no significant differences were noticed between both groups. This finding has not been published elsewhere with the use of ketotifen even for a longer period as for 28 weeks (Volovitz *et al.*, 1988) for 32 weeks (Canny *et al.*, 1997) for 36 weeks (Shakya *et al.*, 2003; Govil and Mirsa, 1992).

Logical explanation for this finding is most likely related to its physicochemical properties & pharmacokinetic profile since ketotifen is, as montelukast, extensively metabolized in liver to active (nor ketotifen) & inactive metabolites (N-glucuronide) that might induce hepatobilary toxicity especially when given for such prolonged period as in our study. Besides this, ketotifen has known to inhibit hepatic microsomal enzymes that add impact on many drug interactions & drug toxicity (Grahnén *et al.*, 1992).

ALT serves as a fairly specific indicator of liver status. Our results indicate that montelukast had no significant adverse- effect on the liver for two consecutive visits after treatment compared to pretreatment values but after 3rd & 4th visits, a significant reduction in ALT activity was shown indicating that its harmless effect on liver.

On the other hand, the ALT activity in the control group shown to increase from the first visit & onward although still it is less than the upper normal limit of 40 U/L (Behrman *et al.*, 2003) & so a significant differences were found between montelukast & control group at the last visit. The elevation in ALT activity is shown correlated with asthma severity and has been attributed to insufficient gas exchange and subsequent liver hypoxia and liver cell damage (Carlos *et al.*, 2001).

An elevation in AST seen after montelukast treatment beginning from the first visit after treatment & forward when compared to pretreatment activity is as has been proposed an indication of liver damage as such results were also reported after montelukast treatment (Khan and Hashmi, 2008).

Ketotifen once daily treatment for 16 weeks had no significant effects on ALT & AST activity compared to pretreatment values & when compared to those pretreatment values throughout study period indicating lack of hepatotoxic effect but when compared with control group a significant elevation was found at the third visit in ALT and after the second visit & onward in AST values. This may be because these values were at the first place higher in ketotifen group patients than in those of control group patients.

Similarly no significant differences were noticed between ketotifen & montelukast group in AST values throughout study period but significant differences were noticed until the fourth visit after treatment in ALT values. This is because ALT activity was reduced in montelukast group but not in ketotifen group.

Estimation of IgE level provides evidence in support of atopy (Chowdary, 2003). In our study we observed a significant reduction in specific IgE values following montelukast treatment which indicates that montelukast was highly effective in attenuating the pathological events associated with IgE-mediated inflammation since it reduced the IgE values from the first visit of treatment & further more reduction thereafter was persisted until the end of the trial when compared to pretreatment value although a study by (Stelmach *et al.*, 2002) revealed that children required high doses of montelukast to reduce IgE levels significantly & proposed that perhaps long-term treatment with montelukast will be beneficial to asthma patients to

decrease IgE levels. We observed that there was a correlation between reduction in specific IgE levels & eosinophils percentage since these two factors contributes to hypersensitivity reactions as well as asthma (Sunyer *et al.*, 1997) however, no significant correlation between the clinical response to montelukast and serum IgE levels was observed after treatment with montelukast for four weeks by (Cai *et al.*, 2006).

Ketotifen showed to be less effective than montelukast in inhibiting this immunoglobulin as no significant differences was obtained after ketotifen treatment for 3 visits & only became significant after the fourth visit. Similar finding was also reported for lack of ketotifen effect on IgE values in asthmatic children & for inhaled steroids also by (Turktas *et al.*, 1996). The low potency of ketotifen in reducing IgE levels indicates that treatment with ketotifen can inhibit mast cells to degranulate in a non-mediated IgE fashion (Castillo *et al.*, 1991).

Another proposed explanation is that ketotifen has no affect on the mast receptor expression for IgE & therefore, the possible mechanism of action of ketotifen could be directed toward the interior of, rather than the exterior of the plasmatic membrane (Castillo *et al.*, 1987).

It has been found that montelukast was more effective in children with higher blood levels of eosinophil cationic protein in their pretreatment blood sample than do children with no response (Kopriva *et al.*, 2003) which may be explained as that montelukast has high influence on IgE-mediated hypersensitivity condition (Tug *et al.*, 2009) & as the children in our study had previous history of atopy coupled with their family's history of atopy therefore montelukast produced satisfactory response in the studied children.

It has been postulated that when decision is made to start regular anti-inflammatory prophylactic treatment, it is based not only on the results of pulmonary function tests, asthma symptoms, bronchodilator requirement, but must be also on the evaluation of the inflammatory markers such as IgE (Fahy, 2000) & that is why use of medication that reduce IgE levels has been considered as effective therapy of asthma (Bradley, 2004). Thus according to our results we can see that montelukast possessed higher efficacy & potency in ameliorating the allergic manifestations in asthma pathogenesis in the studied children than did ketotifen although no significant differences were shown between these 2 groups for 3 visits until the last visit but still we can observe there is fluctuations in IgE values after ketotifen treatment whereas montelukast produced a steep reduction in IgE values starting from the first through the last visit after treatment.

Adverse-effects with montelukast treatment were experienced in 19 out of 40 children and ranged from agitation (28%) to lip edema (2.5%).

Montelukast treatment was associated with agitation which was recognized in 28 % of patients out of 40 children. This adverse CNS stimulation effects was also reported following montelukast treatment by others (Brunlöf *et al.*, 2008; Manali and Wood, 2009; Wallerstedt *et al.*, 2009). Although conflicting results was also stated that montelukast treatment was associated with depressive modes (Dukes and Aronson, 2000). Anyhow, in the absence of confirmed studies concerning these diverse CNS effects, we could not postulate a hypothesis for it, but reviewing montelukast pharmacodynamics with its ability to traverse blood brain barrier (Pardridge, 1999; PRICE, 2000). The documentation of presence of Cyst LTs receptors in the dorsal root ganglia (Evans, 2002; Gennaro et al., 2004). plus that a recent article elucidated potency of montelukast in the prevention of tumor cell migration through both cerebral and peripheral capillaries (Nozaki *et al.*, 2010) gives an indication for a role of montelukast in brain biochemistry.

Thus, from the adverse-effects recorded in the patients in our trial & with those proposed effects of montelukast on the brain we do believe that montelukast in some patients under unusual circumstances can cause neurological disturbances or modulation of excitatory &/ or inhibitory neurotransmission in the brain leading those above mentioned adverse-effects. Of course, these entire mentioned hypotheses are just speculation & certainly require serious attention & approval.

The other adverse-effects (nasal irritation, skin rashes & lip edema) have been also recorded in other studies (Knorr *et al.*, 2001; Minciullo *et al.*, 2004; McEvoy, 2007; Brunlöf *et al.*, 2008). Although numerous studies indicated that montelukast is well tolerated with a safety profile similar both in adult and pediatric populations (Dempsey, 2000) and demonstrated no clinical or laboratory difference in adverse effects versus placebo (Lagos and Marshall, 2007; Bisgaard *et al.*, 2009; Giudice *et al.*, 2009).

Apart from agitation, these adverse-effects are considered mild & unfortunately are expected with any medication especially with a drug that interfere with components of hypersensitivity (Fall and Kopec, 2010 ; Mastalerz and Kumik, 2010).

Ultimately, these adverse-effects were subsided within times after drugwithdrawal, but still they require special attention and may necessitate drug discontinuation.

However, more serious adverse-effects have been published following montelukast treatment as swelling of the face, tongue, lips, eyes, hands, feet, ankles, or lower legs but none of these, other than lip edema, were observed in the children under the present trial.

An interesting adverse-effect is that 8% of the children had increased appetites. Such finding has not

been reported previously and is considered in our opinion a positive outcome. In the mean while, with the absence of postulated hypothesis for this effect we may explain this on the basis that those children either had relieved from asthma symptoms & returned back turn normal appetite (caught up) or that montelukast may stimulate appetite, same as antihistamines, since it can access brain but still it remains unexplainable for the present time & might worth more extensive investigation.

Sedation was experienced in 47% of children enrolled in ketotifen treatment group which was persisted up to 4 weeks after drug discontinuation. This adverse-effect accompanied with ketotifen treatment considered common adverse-effect of ketotifen as other H1-antihistamines (Caps, 1991; Katzung, 2004; Schwartzer *et al*., 2004). The reason is that H1-antihistamines owing to their chemical structure which is derived from the same stem of anticholinergic, antimuscarinic, antidepressants, and antipsychotics agent (Emanuel, 1999; Church *et al*., 2010) and so they have poor receptor selectivity and often interact with receptors of other biologically active amines causing antimuscarinic, anti-α- adrenergic and antiserotonin effects (Govil and Mirsa, 1992; Martin and Romer, 1993). As first generation H1-antihistamines readily penetrate the blood–brain barrier (Yanai *et al*., 1995; Yanai *et al*., 1999; Okamura *et al*., 2000; Szefler *et al*., 2005) & have tendency to interfere with neurotransmission by histamine at central nervous system - H1-receptors so that they causes potential sedation, drowsiness, and somnolence (Holgate et al., 2003; Casale *et al*., 2003) although this was not followed by impaired performance (Barbier and Bradbury, 2007).

The increase in appetite that was experienced by 30% (within 36 children) of patients in ketotifen group is also well known adverse-effect associated with ketotifen treatment that lead ultimately to weigh gain as was found in our trail (Tantichaiyakul and Preutthipan, 2010). The reason for ketotifen causing increase in appetite is attributed to various factors and anticholinergic effects are among one of these (Nematia *et al*., 2006) but studies have related weight gain following ketotifen treatment in patients with elevated TNF-α infected with HIV & AIDs to the ability of ketotifen to inhibit the release of TNF-α (Ockenga *et al*., 1996; Nevzorova *et al*., 2001). Interestingly sedation & increase appetite effects were disappeared after one month of ketotifen withdrawal.

Skin rashes that was experienced in 8.3% after ketotifen treatment was considered minor as it subsided within 4 days after treatment & nasal irritation that was experienced in 5.5 % of ketotifen group patients could be due to sequences of antihistaminic effects of this drug and although it disappeared after three weeks of drug withdrawal but from medical safety point, it should not be ignored & however require follow up.

Since long time ago & so far, considerable studies have proposed that asthma causes growth retardation (Abrams, 2001; Cohen *et al*., 2004) whereas other studies states the opposite & presume that growth retardation is related to asthma severity (Ismail *et al*., 2006). In the present study, although the mean weight percentile of the 102 children was within the range of healthy weight (5th percentile to less than the 85th percentile) but this does not reflect the absence of asthma burden.

The significant increase in weight percentile shown after the first visit of montelukast treatment and onward when compared to those before treatment & to those of control group patient from the second visit & onward indicates that montelukast had positive outcome on improvement of pulmonary function and suppressed exacerbations of asthma symptoms in the studied children as that these children, more likely resumed better appetite that ultimately caused the steady significant increase of weight, a phenomena referred to as caught up effect and indeed 8% of children experienced increase appetite. To our knowledge, such finding has not been reported previously with montelukast but on the contrary researches have showed no influence of montelukast on weight in children (Garcia *et al*., 2006; Becker *et al*., 2006) this finding requires more investigation.

Similarly, ketotifen showed gradually slow increase in weight starting from the first visit to the last visit after treatment compared to those before starting treatment. Such finding has also been stated previously since ketotifen has a property of stimulating appetite that is associated with weight gain (Tantichaiyakul and Preutthipan, 2010). This property is related to its chemical structure which is derived from cyproheptadine, a serotonin and histamine antagonist known to be primarily indicated for increasing appetite & body weight (Grant *et al*., 1990; Nemati *et al*., *2006*). Similar results are reported by (Herbarth et al., 1993) furthermore the role of ketotifen in inhibiting TNF- α that was associated with gained weight in subjects (+ 2.7 kg) after ketotifen treatment has been postulated(Ockenga *et al*., 1996).

The insignificant differences between montelukast & ketotifen effects on weight gain percentile throughout study period reflects the efficacy of both drugs in improving pulmonary function & relieving asthma symptoms that eventually lead to weight gain.

On the contrary, control group children showed significant reduction in their weight at the first visit to the end of treatment protocol. Such finding coincided with those denoting the negative influence of asthma on body linear growth and that growth retardation could be normalized by controlling the allergy (Martin *et al*., 1981; Solé *et al*., 1991; Neville *et al*., 1996; Ismail *et al*., 2006).

VI. Conclusion

1. Distribution of asthma was higher within boys than girls, equally distributed between preschool and in school children, in child's with own history of allergic rhinitis than history of atopic dermatitis and in children with maternal history of allergic rhinitis than paternal history of allergic rhinitis & asthma.
2. Montelukast, compared to ketotifen & control, proved significantly higher efficacy in the treatment of children with mild persistent asthma by improvement in PFT asthma symptoms & the reduction in eosinophils percentage & S.IgE values.
3. Montelukast produced no significant elevation in ALP compared to ketotifen and control patients.
4. Both montelukast and ketotifen produced the increased weight gain.
5. The most prominent adverse-effects noticed after montelukast was agitation whereas sedation was more noticed in ketotifen group patients but disappeared after drug withdrawal.
6. Ketotifen had shared improvement in PFT and asthma symptoms compared to control patients groups.

VI. Recommendation

The followings are recommendations for further investigation extracted from the core of the present study:

- Use of montelukast in the treatment of mild persistent asthma in children.
- Combination of montelukast with ketotifen in treatment of mild persistent asthma.
- Evaluations of montelukast efficacy in adults using PEF & measurement of exhaled nitric oxide levels.
- Investigating the effect of montelukast on S.IgE at different age group in children.
- Investigating the mechanisms of hepatotoxic effects of montelukast.
- Investigating the mechanisms of psychiatric influence of montelukast.
- Investigating the mechanisms of weight gain effect of montelukast.

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