TOWARDS PRAGMATIC TRIALS IN BRONCHIAL ASTHMA

THESIS

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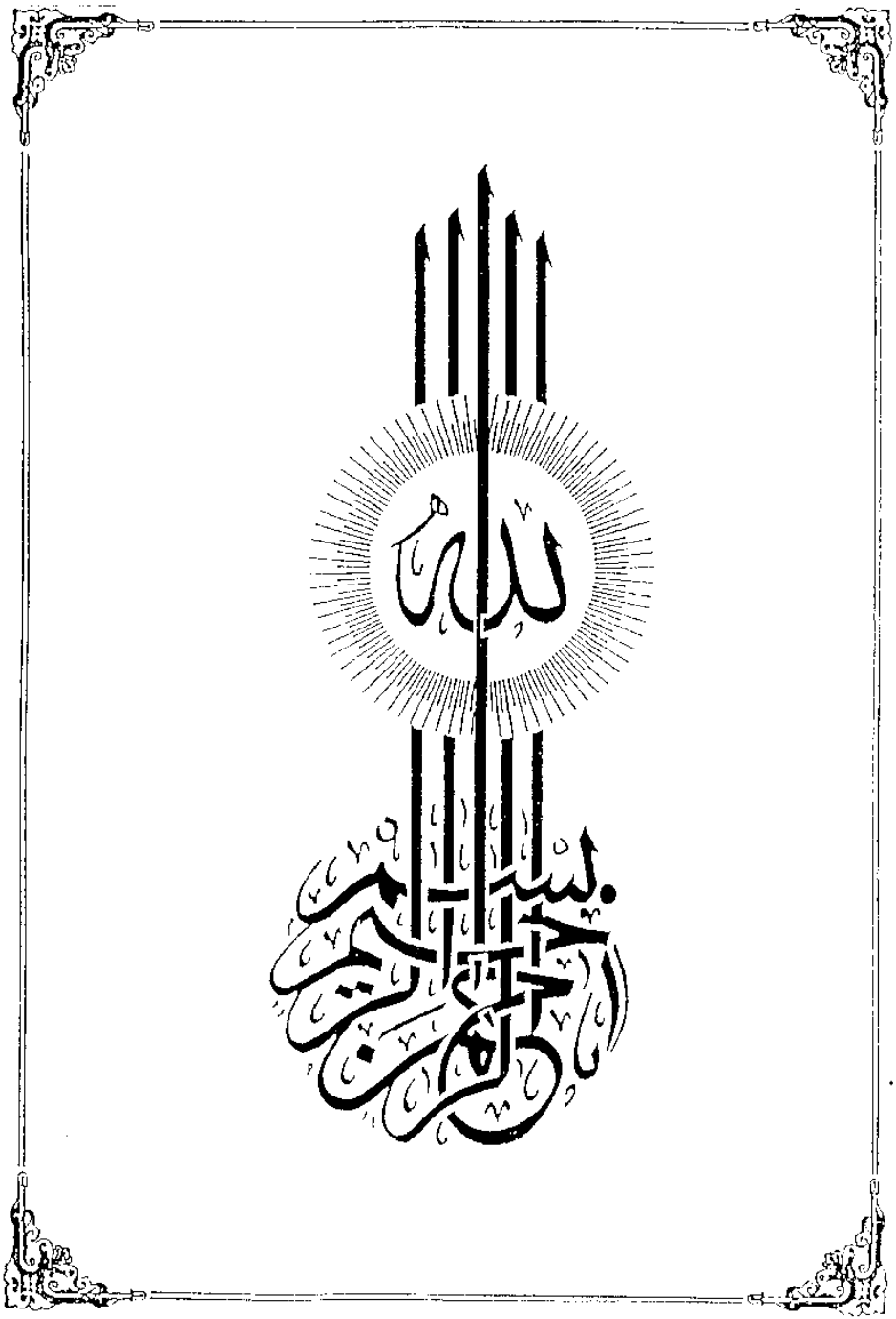

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INTRODUCTION

Morbidity and mortality from asthma have increased over the past decade despite improved understanding and significant advances in medical therapeutics *(Janice et al., 1992)*.

This increase in morbidity and mortility from asthma increases the benifit of pragmatic trials in bronchial asthma.

The aim of pragmatic trials is to determine the place of a drug in the management of a disease and improve medical decision making *(Lurie et al., 1991)*.

The goals of the long term management of asthma is to find the minimum treatment that control symptoms allow resumption of normal life, prevent severe attack and death and control airflow obstruction *(Lurie et al., 1991)*.

AIM OF THE WORK

The aim is to conduct a comparative pragmatic drugs trial in patients with bronchial asthma.

This pragmatic trial aims to provide the scientific basis for determining the place of drugs in management of patients and for improving the medical decision making.

REVIEW OF LITERATURE

BRONCHIAL ASTHMA

Definition:

Asthma is an inflammatory lung disease involving reversible airway obstruction. The characteristic features of asthma include eosinophilia, nonspecific bronchial hyperreactivity to inhaled spasmogens, airway epithelial damage, mucosal edema and mucosal gland hypersecretion. *(Goldie, 1990).*

From the pathological point of view asthma is considered as a syndrome in which different stimuli promote the final common event of bronchoconstriction caused by: (1) airways smooth muscle contraction, (2) mucous hypersecretion, and (3) regional inflammation of major resistance airways; so to define asthma as a bronchospasm is to neglect the additional causes of airways obstruction*(Leff, 1982).*

Scading (1983), defined asthma as a disease characterized by a wide variation over short period of time in resistance to flow in pulmonary airways.

The United National Tuberculosis Association produced

the definition of asthma as a disease characterized by an increased responsiveness of the airways to various stimuli manifested by difficulty of breathing due to generalized narrowing of the airways. This narrowing is dynamic and changes in degree either spontaneously or because of therapy. *(Nicholas, 1980).*

Ciba foundation *Guest* symposium (1959) suggested the following definition: asthma refers to the condition of subject with widespread narrowing of the bronchial airways, which changes in severity over a short period of time either spontaneously or under treatment, and is not due to cardiovascular disease. The clinical characteristics are abnormal breathlessness, which may be paroxysmal or persistent wheezing, and in most cases relieved by bronchodilator drugs including steroids.

PATHOGENESIS OF ASTHMA

Asthma is a multifactorial complex disease. Several factors must be fulfilled to understand the pathogenesis of bronchial asthma.

These factors include:

(1)Immuno Pathologic mechanism in asthma.

(a) the early asthmatic response (EAR).

(b) the late asthmatic response (LAR).

(2) The role of inflammation in asthma.

(a) different inflammatory cells in asthma.

(b) different Mediator release.

(3) Autonomic Nervous System Abnormalities and asthma.

The immunopathologic mechanism in asthma:

After inhalation of allergen,the sensitive asthmatic patient developed an air way obstruction which is variable in time, course, severity and sensitivity to preventive or curative drugs.

The early asthmatic response (EAP).

It begins between 10-30 minutes after the challenge and resolves spontaneously within 1-2h and more rapidly after the administration of beta$_2$ agonist. Its severity depends on the level of immunoglobulin E(IgE), the nonspecific bronchial reactivity to histamine or metacholine and the dose of inhaled Antigen. (Howarth et al., 1985).

When bronchoalveolar lavage (BAL) is immediately performed, the cell population is mainly represented by mast cells and alveolar macrophages. Those cells are rapidly activated by allergen and release mediators. (Hargreave and Fink, 1986).

Two hours after inhalation challenge, there are no inflammatory cells (such as eosinophils or increased number of lymphocytes) in BAL fluid *(Godard et al., 1991).*

This phase is known to be prevented or attenuated by beta$_2$ agonists, theophylline, Anti-H_1 drugs (McIntyre and Boyd, 1984).

The Late Asthmatic response (LAR)

It begins between 2-4h after challenge, peaks at 4-6h. The

time course of airway obstruction is slower and the obstruction resolves during several hours *(Cartier et al., 1982).*

Factors influencing the existence or the severity of LAR are unknown however, it has recently been shown by *Sasaki et al.(1987)* that cortisol depletion increases the occurrence of LAR in dogs.

Inflammatory cells (mainly eosinophils) are present in the BAL fluid 6h after the challange, they are still observed 24-72h later *(Diaz et al., 1989).*

Eosinophils appear to be the most prominent and important cells in human allergic LAR. Neutrophils may be also of relevant importance. *(Fabbri et al., 1987).*

The prevalence of LAR may be higher in children but the reason for this is not known *(Godard et al., 1991).*

More recently it has been shown that the late onset inflammatory component associated with allergy skin testing may be solely dependent on IgE Antibody. These studies support a central role for the mast cell as an initiator of not only immediate tissue responders but also manifestations delayed in

time as well*(Godard, 1991).*

The Role of Inflammation in Asthma

The investigation of modes of action of clinically effective Anti-asthma drugs taught us much about the pathogenetic mechanism of asthma. The wide and marked efficacy of glucocorticoids in mild asthma is a strong evidence in favour of a primary role for inflammation in this disease *(Persson, 1991).*

Glucocorticoids have taken the attention away from bronchial smooth muscle and have helped us to focus on the role of mucosal/submusosal inflammation *(Laitinen et al., 1985).* Epithelial sloughings a distinguishing characteristic of asthmatic airways. Severe mucosal derangements may be seen in early asthma as well as in severe asthma and may be normalized by treatment with glucocorticoids. There has been rapidly increasing interest in the role of epithelial released factors for the control of airway smooth muscle in asthma *(Bordley et al., 1989).*

Chronic Asthma is not always reversible as it was once believed during the immune response, proliferating fibroblasts deposit extensive networks of collagen which can lead to fibrosis and irrevesible airway obstruction *(Holgate, 1992).*

Different inflammatory cells in asthma

Inflammation is often defineed as the presence of elevated number of inflammatory cells in the airways. This information is sometimes complemented with demonstration of particular cellular mediators in airway or blood liquid.*(Persson, 1991).*

So in our discussion we must cover the major individual role of the following cells: Eosinophils, mast cells, macrophages, neutrophils, platelets, lymphocytes and basophils.

It is difficut to sort out the priorities in this field , perhaps, the single cell hypothesis of asthma are almost as unlikely to be valid as the single mediator hypothesis of the disease.*(Persson, 1991).*

Role of Mast Cells in Asthma:

Mast cells are granular cell located in bronchial lumen, submucosa, near blood vessels, and submucous glands through smooth muscle granules and intra alveolar septa. These locations ensure exposure to inhaled antigen. Exposure of susceptible individuals to antigen leads to production of IgE which is attached by FC portion to specific receptors on the mast cell membrane. Once the mast cells is sensitized by

specific IgE, subsequent exposure to multivalent Antigen resulting in bridging of adjacent IgE molecules leads to a series of reactions ending in mediators release *(Middleton et al., 1981).*

In mast cells there are three distinct sources of mediators :

1) Preformed mediators which are contained in the granule matrix such as histamine. They are released into the tissue fluid immediately.

2) Secondary formed mediators generated by the interaction of primary mediators and nearby cells and tissue. They are formed immediately or within minutes such as leukotrienes.

3) Granule matrix derived mediators, which are performed but not immediately dissociated from the granule. It remains in the tissue for hours until dissolution occurs or they are phagocytosed *(Casale and Kaliner, 1984).*

The events initiated by the mediators depend upon the tissue into which they are released. Thus, histamine in the skin or nose may produce primarily vasopermeability, while in the lung it may also induce bronchospasm.