A COMPARISON BETWEEN A COMBINATION OF IPRATROPIUM BROMIDE PLUS SALBUTAMOL AND IPRATROPIUM BROMIDE IN BRONCHIAL ASTHMA

THESIS

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By
OMAR IBRAHIM OMAR
M. B. ; B. Ch.

Supervisors
Prof. Dr. YEHIA MAHRAN
Professor of General Medicine
Prof. Dr. MOHAMED AWAD TAG EL-DIN
Assistant Professor of Chest Disease
Prof. Dr. MOHAMED RAMADAN
Assistant Professor of General Medicine

Faculty of Medicine
Ain Shams University

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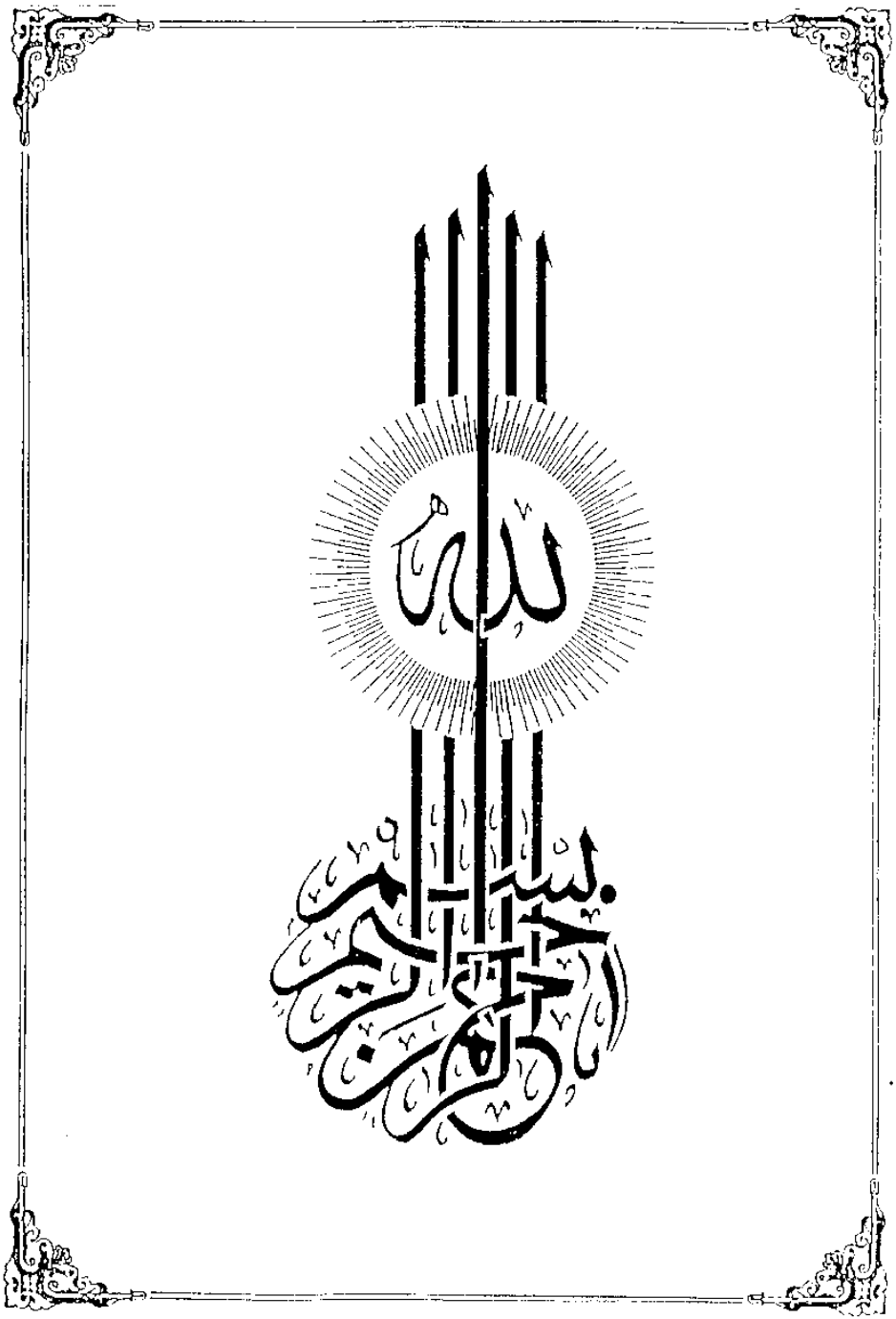

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INTRODUCTION

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It has been suggested that cholinergic mechanisms may be involved in the pathogenesis of asthma (Simonssen et al., 1967).

A theoritical advantage of a combination of bet-stimulants and an anticholinergic agent therefore exists (Barnes et al., 1980).

Ipratropium bromide is a synthetic anticholinergic bronchodilator shown to be of use in acute and chronic asthma.

REVIEW OF LITERATURE

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Bronchial Asthma

Definition

Definitions of what constitutes bronchial asthma still vary very greatly, and the reason for this is to be found in the still limited knowledge of the aetiology and pathogenesis of asthmatic disease (Herzog,1982).

In 1962, Meneely et al. wrote;"Asthma is a disease of the respiratory passages characterized by dyspnea of an obstructive type which is predominantly expiratory, reversible at least partially and of varying severity and duration".

On the other hand, in 1967 the United States National Tuberculosis Association produced the definition:"Asthma is a disease characterized by an increased responsiveness of the trachea and bronchi to various stimuli and made manifest 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. The basic defect appears to be an altered state of the host".

The altered state mentioned at the end of this definition refers to the hyperreactivity of the bronchial system, a

feature common to all patients with obstructive disease of the airways. (Herzog, 1982).

Clinical types of asthma

Two subgroups of asthmatics can be defined:

1. Those in whom there is a history of extrinsic (or external) factors provoking their attacks, and
2. Those in whom no such provoking agents can be identified (cryptogenic or intrinsic asthma) (Rackemann, 1947).

Extrinsic asthma:

Extrinsic asthma due to a specific external allergen can be subdivided according to whether the subject is atopic (i.e. manifest by demonstrable type I skin reactions to astandard range of common allergens) or not. (Turner Warwick, 1978).

The nature of atopy :

In 1916, Cooke and Vander Veer described human protein sensitization in a group of 621 patients suffering from asthma, apparently due to exposure to animals and

various foods. They noted a familial incidence in 48 percent. They suggested that allergic individuals possesed the capacity to become sensitized to certain proteins to which they are exposed.

Coca and Cooke (1923) proposed that the term atopy should be used to describe such individuals. Grove and Coca (1925) described specifically reacting substances in the serum of atopic individuals and termed these "atopic reagins". These serum factors were shown to be immunoglobulin E (IgE) (Ishizaka et al., 1966, Johnsson et al., 1968, World Health Organization, 1968).

Pepys (1975) has suggested a redefinition of atopy as that form of immunological reactivity of the subject in which reaginic antibody, now identified as IgE, is readily produced in response to ordinary exposure to the common allergens of the subjects environment.

The immunological identification of these individuals can be made from skin tests or serology.

The other subgroup of extrinsic asthma namely non-atopic extrinsic asthma is that in which patients develop their symptoms in relation to some particular agent. Often after excessive exposure. (Turner-Warwick, 1978). These

patients have negative skin tests to the standard range of common allergens but may show an immediate, late or dual response to the specific sensitizing agent. There is evidence to suggest that non-IgE reaginic antibodies may contribute to immediate hypersensitivity reactions in a minor proportion of patients with extrinsic asthma. (Parish, 1973). A heat stable short-term sensitizing (STS) IgG antibody has been demonstrated in some patients with "immediate" extrinsic asthmatic reactions to the house-dust mite. (Bryant et al., 1973). These subjects are usually non-atopic and their reactions may not respond to sodium cromoglycate.

Intrinsic (cryptogenic) asthma:

Patients presenting with typical asthma and no evidence of extrinsic allergen from the clinical history and prick testing with common allergens, have been classified as intrinsic (Rackemann, 1947).

The term cryptogenic is perhaps more appropriate in that it implies that the causal agents are quite unknwon at the present time (Turner, Warwick, 1978).

There is considerable evidence that reaginic antibodies are not involved, and a normal total serum IgE

has been reported in several series of patients with cryptogenic asthma. (Johansson, 1967; Assem et al., 1971; British Tuberculosis and thoracic ass.,1975). Specific IgE in serum, to the common allergens in the United Kingdom namely gross pollen and dust, is absent (Stenius et al., 1971).

Ford (1969) defined intrinsic asthmatics as those patients who had strong association with upper and lower respiratory tract infections, non allergen associated or with unknown factors.

Unspecific physicochemical stimuli can irritate the bronchial system and produce by reflex action an increase in the tone of the bronchial musculature. (Herzog, 1982).
As with many other conditions, there tends to be a spectrum between the two polar groups. (Cole, 1977).

Pathogenesis

One feature which distingishes all asthmatics and can identify an asymptomatic asthmatic, is the phenomenon of bronchial hyper-reactivity, where bronchoconstriction greater than 15% follows inhalation of an irritant e.g. sulphur dioxide, cold air, histamine or the acetylcholine analogue methacholine (Boushey et al., 1980).

Exogenous factors in bronchial hyper-reactivity:

a) Allergy:

In the case of an atopic individual, antigens like flower pollen, animal fur, or bird feathers induce the formation of antibodies of the immunoglobulin E type, which attach themselves to the surface of mast cells in the bronchial wall, and of basophilic leucocytes circulating in the blood. Re-exposure to the antigen activates enzyme systems in these cells which trigger the immediate release of anaphylaxis - mediators such as histamine, or the synthesis of other transmitter substances such as the slow - reacting substances of anaphylaxis (SRS-A) (Gold, 1975). These substances in turn cause acute obstruction of the bronchi within a few minutes. (Lane and Storr, 1979).

In the light of recent research (Nadel, 1977),(Gold 1975), the traditional conceptual model of allergic asthma, which postulates a direct action of the mediator substances on the muscles and tissue cells of the bronchial wall, is no longer tenable. The results of these studies suggest that the major part of the mediator action is to be explained in the term of the activation of parasympathetic neurons is the form of vagal reflex. (Gold, 1973).

In fact, de Kock has demonstrated, together with Nadel and Colebatch, that cooling or transsection of both vagal nerves at the neck in dogs under general anaesthesia almost totally prevents the airways constriction provoked by the injection of histamine into the bronchial arteries (Gold, 1975).

b) Infection:

It has been shown that the proteolytic enzyme released by bacteria or leucocytes sensitize the parasympathetic receptors of the airways, that is to say, produce an effect identical with that characteristically exerted by the mediators released during the antigen - antibody reaction by mast cells and basophilic leuococytes. Against this background it is easy to understand the often drastic deterioration in the condition of such patients after bacterial infection, usually persisting long after the infection, Itself has been successfully treated by chemotherapy. (Herzog, 1982).

c) Non-specific physicochemical stimuli:

Non-specific mechanical, thermal and chemical stimuli can irritate the bronchial system, produce a reflex increase in the tone of the bronchial musculature. This

vagal reflex starts at irritant receptors in the bronchial airways, these receptors are pressed between the mucosal epithelial cells, and terminate just beneath the very tight junctions where the cells are in contact with the mucous layer in the lumen, afferent fibres lead back to the central nervous system through the vagus, and stimulation of these irritant receptors leads to a reflex increase in effector parasympathetic activity, which in turn causes contraction of bronchial smooth muscle with coughing and increased mucus secretion (Phipps, 1981).

Recent investigations have shown that, in its turn, the acetylcholine released simultaneously stimulates the sensory receptors, investigates a new reflex and thus sets up a vicious circle. The strength of the reflex response, which is automatically intensified by this bioamplification loop, is modulated by higher brain centres, especially the reticular and limbic systems, which in their turn receive impulses via extrapulmonary afferent nerves and from emotional factors. (Ziment, 1978).