A STUDY OF B - AGONIST DRUGS IN COMMON USE ON PULMONARY FUNCTION TESTS IN ASTHMATIC EGYPTIAN CHILDREN USING VITALOGRAPH

Thesis submitted
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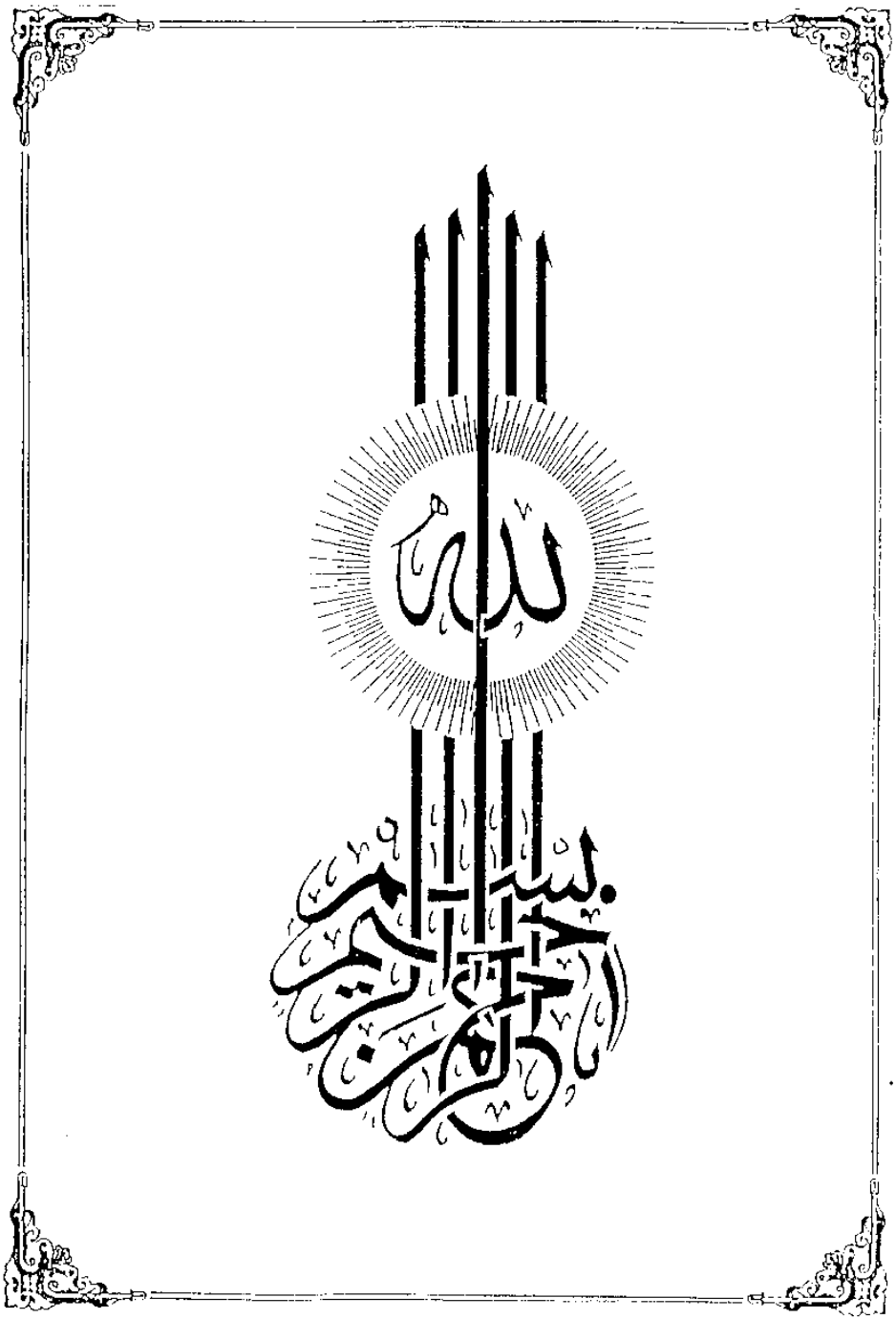

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INTRODUCTION

Asthma is leading cause of chronic illness in childhood. It is responsible for a significant proporation of school days lost because of chronic illness.

Also asthma can lead to sever psychological disturbances in the family.

During acute attacks of experimentally-induced asthma, the predominant site of induced constriction may be either in the central or peripheral airways. During remission between spontaneous asthmatic attacks, there is evidence that considerable obstruction may be present in peripheral airways. Although other studies showed that acute constriction of the central airways may be mediated by a vagal reflex mechanism, the pathophysiology of peripheral airways obstruction in asthma is less well understood and may be caused by mucous secretions, edema, inflammatory exudates, fibrosis and/or bronchospasm with varying degrees of revesibility in reversible obstruction airways

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disease either the large or small airways may be the major site of obstruction, in contrast to chronic irreversible obstructive airway disease in which the small airways are nearly always principally involved. In further studies of maximal expiratory flow responses to helium-oxygen breathing in asthmatic subjects. It was found that the large airways were the major site of obstruction in those asthmatic subjects without a history of cigarette smoking, chronic bronchitis or repeated respiratory tract infection, whereas the small airways were principally narrowed in asthmatic subjects in whom these factors were present. These workers pointed out, however, that the predominance of obstruction in the large airways of some asthmatic subjects does not exclude the presence of peripheral airways obstruction and that obstruction in small airways is not necessarily irreversible. (Tashkin et al., 1980).

With proper treatment, however much relief can be provided. Long term maintenance therapy of asthma with B adrenoceptor stimulants is commonly practiced in Europe. These drugs can be administrated in several forms.

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The aim of this work is to study the effects and side effects of an adrenergic B stimulants.

Also comparison between drugs and routes of administration of B adrenoceptor stimulants will be discussed.

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REVIEW OF LITERATURE

B agonist drugs:

It has been suggested that the B receptor is either actually located on the enzyme adenyl cyclase or is closely associated if not an integral component of the adenyl cyclase system itself i.e. according to one hypothesis the B receptor is an integral part of adenyl cyclase system. However other investigators tend to favour the view that the B adrenergic receptor is a separate entity from adenyl cyclase and that adenyl cyclase is only one of the many systems that are affected by it.

Activation of both B_1 and B_2 receptors results in activation of adenylate cyclase and increased conversion of ATP to cAMP. Activation of the cyclase enzyme is mediated by a stimulatory guanine nucleotide-dependant coupling protein similar to the inhibitory "N" protein identified with certain α_2 receptors. cAMP is the major "second messenger" of beta receptor activation (Hoffman, 1986).

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Stimulation of B_1 receptors produces:

a- increase rate of heart through action on S.A node (chronotropic action).

b- increase force or increase contractility (inotropic action).

c- increase conduction velocity and shortening of functional refractory period (arrhythmogenic action).

Stimulation of B_2 receptor produces:

a. vasodilation chiefly in skeletal muscle, and coronary bed.

b. bronchial relaxation.

c. uterine relaxation.

d. Intestinal relaxation (in the intestine both α and B_2 recptoros exist leading to intestinal relaxation.

Examples of B agonist drugs on common use:

(1) **Isoproterenol (Isuprel):**

Isoprenaline has comparatively short bronchodilator action because it is rapidly metabolized by the enzyme catechol-O-methyl transferase, moreover,

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in addition to being a powerful stimulator of B_2 adrenergic receptors leading to bronchodilatation it also stimulates B_1-receptors in the myocardium, leading to tachycardia and a rise in cardiac output (Aviado and Schmidt, 1957; Kelman et al., 1969). This side effect is due to a direct result of the cardiac effects. Hypoxaemia may become worse after isoprenaline even though airway obstruction is diminished, when large doses are given, particularly when the patient is hypoxaemic, serious cardiac complications such as venticular fibrillation or ventricular asystole may occur. The recent rise in asthma mortality coincided with the widespread use of portable pressurised aerosols containing most frequently, isoprenaline and it is relatively inactive orally and is usually administrated by inhalation as aerosol of (1:100 or 1:200 aqueous solution) or it is administered via subcutaneous injection route or sublingually (Jegge et al., 1971).

(2) **Metaproterenol (Alupent):**

Metaproterenol possesses slightly more $beta_2$ specifity than does isoproterenol, but again, still exerts some $beta_1$ activity. It is marketed for oral

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use (0.5 mg/kg/6 hrs.), S.C. injection and aerosol administration (Lefcoe et al., 1982). Studies involving aerosol administration of metaproterenol to asthmatic children generally report greater improvement in pulmonary function and a longer duration of action than isoproterenol (Passamonte and Marting, 1984).

(3) **Isoetharine (Bronkosol):**

Isoetharine is not much more selective beta agonist than isoproterenol. It is less potent than isoproterenol, It has a shorter duration of action (Galant, 1983). Isoetharine is used in the aerosol form.

(4) **Terbutaline (Bricanyl):**

Fortunately, small chemical changes in the isoprenaline molecule have lead to a series of related compounds which have to a large extent overcome the disadvantages of isoprenaline. Substitution of other groups or rearrangements of the existing groups in the benzene ring have rendered the compounds more resistant to the action of catechol-O-methyl transferase, thus prolonging their action, changes

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in the side chain have increased their specificity for the B_2 or bronchial as opposed to the B_1 or cardiac receptors. A dose of (0.075 mg/kg) is administered orally 3 times daily, subcutaneously (0.25 mg) or as an aerosol (1 mg/ml dilution) and all of them produce marked improvement in ventilatory function over a few hours span. (Legge et al., 1971).

(5) **Salbutamol (Ventoline):**

Salbutamol has beta$_2$ adrenergic selectivity similar to that of terbutaline. It can be administrated orally (0.2 mg every 6-8 hours), subcutaneously (1.75 mg/kg) or as an aerosol (Palmer et al., 1970). The bronchodilator effect of salbuamol was greater when patients received nebulized salbutamol. Its side effects are similar to those of terbutaline. (Grimivood et al., 1981).

(6) **Fenoterol (Berotec):**

Modern selective B_2 receptor stimulator Fenoterol play an important role in the treatment of bronchial asthma. They have a good and dependable clinical effect, and there are no serious side effects were reported. Subjective discomfort due to tremor

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or slight tachycardia may occur but can be handled by dose reduction. This B_2 receptor stimulator is known to have a long duration of action and in clinical trials there is often not a complete return to the initial expiratory flow values even 8 hr after inhalation of the active substance. It can be argued whether the long lasting improvement during daytime is an effect of the bronchialating substance alone or if diurnal variation in bronchial tonus has a strong positive influence on the expiratory flow, thus simulating a long duration of action of the inhaled active substance. (Graff and Lonnevig, 1979).

(7) **Bitolterol mesylate:**

Bitolterol mesylate is a "prodrug" that is hydrolyzed by an esterase which has its highest concentration in the lungs, to a catecholamine with marked selectivity for beta$_2$-adrenergic receptors. It differs from epinephrine in having a large N-alkyl substituent that increases B_2 selectivity. The vulnerable catechol hydroxyl groups are protected by di-p-toulate esters, which decrease susceptibility to inactivation by catechol-O-methyltransferase. These properties result in a high concentration

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of the active drug in the lungs and in prolonged bronchodilator activity with negligible side effects. (Kemp et al., 1984).

(8) **Procaterol:** is a new potent, long-lasting non-catecholamine B_2 agonist which has been developed in Japan. The only significant side effect noted was tremor. (Barbera et al., 1984).

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