Long Acting B2 Stimulants Versus Long Acting Theophylline in Management of Bronchial Asthma

Thesis

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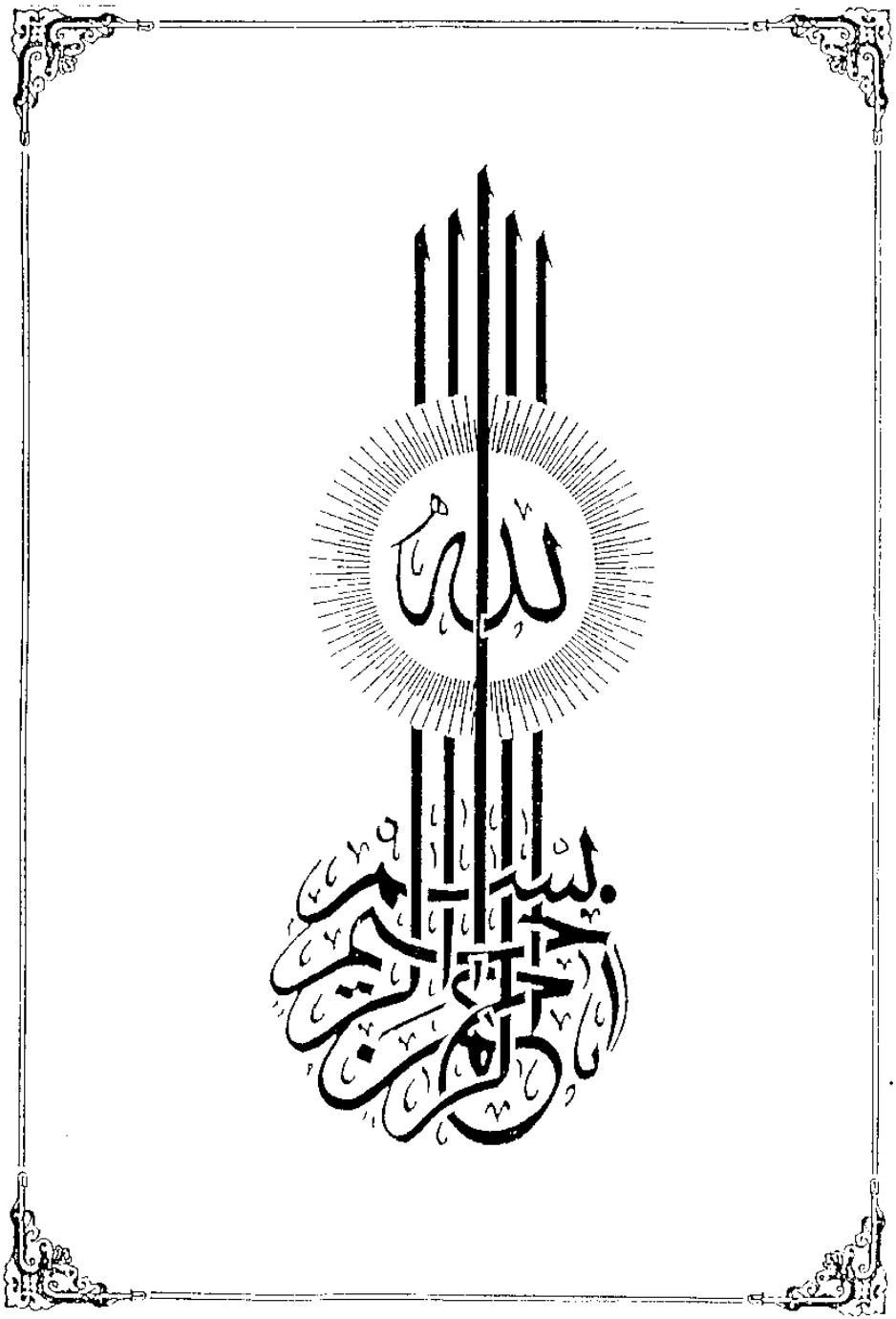
بسم الله الرحمن الرحيم

﴿... قال رب اشرح لى صدرى
ويسر لى امرى واحلل عقدة
من لسانى يفقهوا قولى ...﴾

"صدق الله العظيم"
"سورة طه آيه ٢٥-٢٧"



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Introduction

Introduction

The therapy of Asthma may be conveniently be divided into the use of three types of drugs: broncho-dilators, prophylactic drugs and oral or systemic corticosteroids. Broncho-dilators may be given by nebulizers, aerosols, inhalers, tab, supp, or injection. The best broncho-dilators used by inhalation are those which selectively stimulate B_2 adrenergic receptors in the bronchial wall. The well known B_2 stimulants have a short duration of action ***(Seaton et al., 1989).***

Salmeterol is a new potent selective B_2 adrenoceptor agonist, it has a long duration of action through its mechanism of action by binding to the cell membrane protein which leads to more persistance and effecacy of the drug ***(Bradshow et al., 1982)***. Salmeterol produces presistant bronchodilation, suppression of inflamatory mediators release with long lasting inhibition of vascular permeability, salmeterol is of slow onset and slow offset and has the same side effects of other B2 stimulants ***(Johnson, 1989).***

Oral long acting theophylline signify a major theraputic advances in the treatment of obstructive lung diseases not only in acute asthma but may be in patients with chronic airflow limitation, ***(Johnson, 1982)***. Sustained released theophylline produces bronchodilation, relieve of pulmonary hypertension ***(Bock, 1932)***. Stimulate mucociliary clearance ***(Serafini & Michealson, 1976)***, and improves work of respiratory muscles ***(Aubier, & Machlon, 1981).***

Aim of the Work

Aim of the Work

The aim of this work is to compare between the efficacy of the new long acting B2 stimulant salmeterol and long acting theophylline.

Review of Literature

Asthma Therapy

The aim of drug treatment of asthma is to reduce symptoms and also to reverse, at least in part, the disease process towards normality, smooth muscle cells of the bronchi, mast cells, inflammed cells of local edematous tissue and the cells involved in the production and clearance of mucus are the targets for the drug therapy. ***(Seaton et al., 1989).***

Main lines of asthma therapy:

A. Bronchodilators.

B. Prophylactic drugs.

C. Corticosteroids.

A. Bronchodilators:

1. Sympathomimetics.
2. Anticholenergics.
3. Methylxanthines.

1. Sympathomimetics:

B- adrenoreceptor Agonists:

B- agonist are the most widely used and effective bronchodilators currently available. They are safe, well tolerated, easy to administrate and without significant side effects, ***(Barnes et al., 1986).***

Adrenaline has been used as a bronchodilator since the begining of this century, adrenaline stimulate Alpha and Beta receptors but because the alpha agonist effects limited the dose which could be given, isoprenaline which has only B- agonist effects was vetrated in 1940. Isoprenaline is non selective B- agnoist stimulating both B1- & B2- receptors, but the B1 effect is responsible for cardiac stimulation and in the late 1960s selective B2 agonists, such as salbutamol and terbutaline were introduced ***(Barnes, et al., 1986).***

Mechanism of action:

They bind to receptors in the cell membrane leading to activation of adenylcyclase enzyme and hence cyclic AMP is incived leading to bronchodilation, although direct relaxation of airways smooth muscle is probably their major mechanism of bronchodilation, they may also produce bronchodilation indirectly both by inhibition of cholenergic tone and reducing mediator release ***(Brown et al., 1982).***

Also they may speed the clearance of viscous mucus from the airway. ***(Barnes, et al., 1986).***

Administration:

Inhalation:

B2 agonist may be taken in much variety of ways but the preferred therapy route is by inhalation, as this method produces the desired effect with minimal side effects, inhaled therapy has the advantage of a rapidness

of action so, they act within 3-6 minutes, reaching the peak in 30-60 minutes, with the effect dying over about 3-6 hours. ***(Seaton et al., 1989).***

Oral administration:

Oral therapy produces branchodilation after 30 minutes of administration and reaching the peak at 1-2 hours. It will be noticed that terbutaline and fenoterol have relatively long half-life, so that twice daily dosage may be adequate in some patients. ***(Stewart et al., 1987).***

Parenteral administration:

The B2 agonists salbutamol and terbutaline are both available for parenteral administration in severe exacerbations of asthma. ***(Vandenberg et al., 1984).***

Subcutaneous B2 agonist may be used in severly asthmatic patients ***(Lewis et al., 1987).***

Metabolism & excretion:

Orally administrated B2 agonists tend to undergo some conjugation in the gut wall that are administrated parenterally circulate in the plasma unchanged. Inhaled drugs enter the circulation, but usually only in microgram quantities. Only small quantities of these drugs are excreated unchanged by the kidneys and dosage modification is unnecessary in renal insufficiency. They do cross the placenta however an oral medication is best avoided in pregnancy ***(Seaton et al., 1989).***

Potency:

The potency of sympathomimetic bronchodilators can be expressed in terms of ED 50 meaning the dose (D) that produces as standered measured effect (E) in 50% of subjects, so that the lower the ED50 the greater is the potency. Although the potency of the B2 agonists may vary according to the configurations of the chemical substitutions make the benzene ring and ethanolamine side chain, this is of little practical consequence as the dose contained in one (puff) of a lesser dose of a slightly more potent compared, the same applied to tablet formulations. As: 4mg tablet and 360ug (two puffs) fenoterol by meterd dose inhaler and to 400ug (two puffs) of pibuterol. ***(Repsher et al., 1981).***

Some B2 selective drug members:

These agents differ structurally from epinephrine in having a larger substitution on the amino group and in the position of the hydroxyl groups on the aromatic ring.

Metaprotrenol, albuterol, terbutaline, and bitolterol are available as meterd dose inhaleres, 0.3, 0.5ml of metaprotrenol solution (5%) and albuterol solution (0.5%) can be diluted in 0.3-1.5ml of saline for delivery from a hand held nebulizer. Although adrenoreceptor agonists may be administered by inhalation, oral or parenteral routes. Aerosal deposit depends on the particle size, the pattern of breathing (tidal volume, and rate of airflow), and the geometery of the airways. Even with particles in

the optimal size range of 2-5m um, 80%-90% of the total dose of aerosal is deposited in the mouth or pharynx. Deposition can be increased by holding the breath in expiration ***(Homer, 1992).***

	Oral dose	S.C.	I.V.	IV. IF.	MDI	Nebulizers
Salbutomol	4mg tds	500ug	250	5 ug	100-200 ug	2.5-5 mg
Terbutaline	5mg tds	250	250	5 ug	250-500 ug	5-10 mg
Pirbuterol	10-15mg tds	--	--	--	200-400 ug	--
Reproterol	10-20mg tds	--	--	--	500-1000ug	10-20mg.
Fenoterol	2.5-7.5mg tds	--	--	--	180-360 ug	0.5-2.5mg
Rimiterol	--	--	--	--	200-400ug	--
Metaprotrenol	10-20mg tds	--	--	--	225 mg	0.65 ug.
Bitoteterol	--	--	--	--	0.37mg	--
Salmeterol	--	--	--	--	100-200ug	--
Formoterol	--	--	--	--	100-200ug	--

Adverse effects of B2 agonists:

- Skeletal muscle tremor ***(Lulich et al., 1986).***

- Feelings of restlessness, apprehension, and anxiety may limit therapy with those drugs. ***(Goodman & Gilman, 1991).***

- Tachycardia is a common adverse effect, rarely arrhythmias may occur or myocardial ischemia, however patients with underlying coronary artery disease or arrhythmias are at much greater risk ***(Goodman & Gilman, 1991).***