CHAPTER I

INTRODUCTION

Bronchial asthma is a chronic disease characterized by episodic bronchial obstruction and ventilatory insufficiency and is manifested clinically by wheezing respirations, dyspnea, cough and mucoid sputum production. The essential pathological changes in the bronchi and bronchioles which cause these symptoms are mucosal edema, hypersecretion of a viscid, tenacious mucous and smooth muscle contractions.

Two types of bronchial asthma are recognized clinically: first, extrinsic asthma, for which the immunological, biochemical and pharmacological mechanisms are reasonably well defined; and second, intrinsic asthma, about which the causal mechanisms are poorly understood.

Extrinsic asthma is brought about, in genetically susceptible individuals, by the sequential occurrence of(1) sensitization (usually transmucosal), (2) subsequent re-exposure to antigen with antigen-antibody reaction in the lung, (3) release of pharmacologically active substances by a series of incompletely understood biochemical events, and (4) the action of these substances on blood vessels, mucous glands and smooth muscle in the lung. Although the chain of events leading to intrinsic asthma remain obscure, both types of asthma share essentially the same physiological and pathological features (Middleton, 1965).

The manifestations of immediate-type hypersensitivity reactions appear to result from the release of mediators after the union of antigen with IgE antibody fixed to mast cell membranes. IgE antibody binds selectively to mast cells and basophil leucocytes, and when IgE combines with antigen, a series of events takes place, leading to the liberation of mediators such as histamine, slow-reacting substance of anaphylaxis (SRS-A), and putative mediator such as eosinophil chemotactic factor of anaphylaxis (ECF-A). The biochemical processes linking the antigen-antibody reaction on the cell membrane is not fully understood, but it has been known for some years that calcium is required in the extracellular medium and that metabolic processes within the mast cell must be intact (Foreman and Garland, 1976).

Histamine, one of the important mediators, is released from human asthmatic lungs on contact with specific antigens. It possesses all of the attributes of a potent bronchoconstrictor. It increases capillary permeability, causing mucosal edema, hypersecretion of bronchial mucosal glands and stimulates the contraction of smooth muscles in the bronchial trees (Goodman and Gilman, 1975). Interestingly, histamine provokes asthma only in subjects with the disease (Curry and Lowell, 1948).

Slow-reacting substance of anaphylaxis (SRS-A) was named by Brocklehurst (1953). The smooth muscle contraction caused by SRS-A is delayed in onset, slow and sustained in progression. Unlike histamine, which exists preformed in tissue stores, SRS-A appears to be formed as a result of the antigen-antibody reaction in lungs

(Brocklehurst, 1962). Lung is the only significant source of STS-A (Middleton, 1964). The mechanism of formation of SRS-A is not yet well understood.

The purpose of this study was to investigate whether there was therapeutic benefit in the administration of a minimal dose (200 micrograms) of fenoterol aerosols to relieve bronchial obstruction in asthmatic outpatients.

The problem of evaluating bronchodilator drug response is not what we measure but how we measure (Permutt, 1978). The advantage in evaluating a bronchodilator drug response with a more sensitive test is that, we need fewer replications and/or a minimum dose of the drug to demonstrate a statistically significant response.

The use of a single forced expiration as a method of assessing ventilatory capacity is becoming increasingly popular. The basis of most of the various single-breath methods is the same : the volume of air expired is measured against time by means of a spirometer with either a recording drum or a timing device. It is generally agreed that methods of this kind are clinically valuable. All the methods, however, suffer from the disadvantages that the necessary apparatus is cumbersome and normally requires connection to an electric supply. Attention has therefore been directed to the possibility of using the maximum forced expiratory flow rate (or "peak flow rate") as a measure of ventilatory capacity.

The Wright peak flow meter (Wright and McKerrow, 1959) has

been increasingly used in the last 20 years. It can make use of the fact that, although only a small resistance can be tolerated, an expiration has large volume, so that a very simple and robust instrument can measure changing flows with quite sufficient accuracy.

More recently, the peak flow meter was developed to meet the requirement of general practitioner. Its wide use in general practice revealed that unsuspected impairment of ventilatory function was very common and has played an invaluable part in management of asthma and chronic bronchitis. It has also been used in many studies for evaluating antiasthmatic drugs.

Another instrument, the mini-Wright peak flow meter was designed by Dr. B. M. Wright of the Medical Research Council, Pneumoconiosis Unit, Llandough England. According to the report (Permission from M.R.C.) of Dr. J. F. Frears, Plymouth General Hospital, there was good correlation between mini-Wright peak flow meter and the standard Wright peak flow meter.

Since the introduction of the peak flow meter, many authors have differed in their opinion of its value. Lockhart (1960) found that it separated respiratory conditions with an efficiency equal to that of other instruments in common use such as spirometer. Hoffbrand et al (1966) suggested that the peak flow appeared to be a more sensitive index of changes in airways resistance after bronchodilator drugs than measurements made with a portable bellow spirometer. The work of Anderson et al (1972) indicated that changes in peak expiratory flow rate (PEFR) during and after exercise in asthmatic subjects

have been shown to correlate well with changes in forced expiratory volume in one second (FEV_1).

In this study, pulmonary function test has been studied by using mini-Wright peak flowmeter since it was easy for asthmatic patients to operate during their asthmatic attack.

The use of aerosols in diagnostic tests and in medication has markedly increased in the past decade. Applying drugs in the form of aerosols to patients with respiratory problems is often considered a most direct way to bring a bronchotropic substance to its target area. But there is insufficient evidence for the exact site of deposition of most medicaments in the respiratory tract. How much of the quantity applied is lost by exhalation is not known either. There is also no clear idea about what happens to the medicament itself during its passage along the bronchial trees and after its deposition in certain regions of the respiratory tract.

The main point of the inhalation of a drug is its deposition and pharmacological action, not its deposition and clearance.

Depositing aerosols in the lung is not a simple matter, since the upper respiratory tract, laryngeal region and branching system of airways provide an extremely efficient aerodynamic filter, which prevents an assortment of naturally-occurring biologic and non-biologic particulates from penetrating deeply into the lung and acts as an important pulmonary defense mechanism. It is this same mechanism that makes it relatively difficult to achieve drug deposition in the airways

(Newhouse et al, 1976).

The factors determining aerosol deposition sites in the lungs have recently been reviewed in detail by Morrow (1974). These include particle-related factors such as size, shape and density; and airway-related factors such as flow rate, tidal volume, respiratory frequency and airway caliber. For the comparison of aerosols and the prediction of their deposition sites in the airways, the concept of aerodynamic mass median diameter (AMMD) is useful (Newhouse and Ruffin, 1978).

The AMMD is a measure of the settling velocity of a given aerosol due to gravitational forces, expressed in term of a spherical particle of unit density having the identical settling velocity in the air. The physical principles determining deposition site are related chiefly to aerodynamic particle size and are primarily impaction, sedimentation and brownian movement.

With nasal breathing, the majority of particles in the 5-10 μm. range are deposited by impaction on the turbinates, while, during mouth breathing, the tonsillar area of the pharynx and larynx as well as the initial five or six bronchial bifurcations are the sites of greatest inertial impaction. Smaller aerosol particles (5-0.5 μm.) remain airborne to penetrate beyond the 10th bronchial division and are deposited mainly by sedimentation. Brownian motion or diffusion is the chief determinant of deposition for extremely small particles of 0.1 μm. and below and currently has no therapeutic significance.

The fate of the inhaled aerosol burden is influenced by the

deposition site, physical, chemical and biological characteristics of the particles, efficiency of the mucociliary transport system, and the response of macrophages and other cellular and humoral mechanisms.

Soluble particles such as drugs will be readily absorbed into the blood stream wherever they are deposited, absorption being somewhat more rapid from the alveolar regions (Yeates et al, 1973).

The outpatient treatment of asthma can be a challenging and frustrating therapeutic problem. Finding drugs with maximum benefit, long duration of action, ease of administration and lack of side effects is always of great importance. The adrenergic aerosols have been of great aid with respect to rapid relief of symptoms and the ease of administration. However, major problems with short duration of action, patient abuse and excessive side-effects have limited their usefulness.

There are presently about 14 known beta-2 sympathomimetic aerosols available in the world. The search for more specific beta-2 adrenergic agents was catalyzed by the discovery of two different beta receptors (Lands et al, 1967). Beta-1 receptors increase cardiac rate and force, relax intestinal smooth muscle and stimulate lipolysis. The beta-2 receptors are concerned with relaxation of bronchial, uterine and vascular smooth muscle and the stimulation of glycogenolysis. Thus it becomes evident that the major cardiovascular, central nervous system and gastrointestinal side effects produced by the earlier compounds are mainly secondary to their alpha and beta-1

stimulation, while the desired bronchodilation is due to beta-2 stimulation. With the advancement of new synthetic chemical technics, agents with major or exclusive beta-2 stimulatory effects have been developed.

The general outline of the biochemical basis of action of beta agonists is now quite clear. After binding of the agonists to the receptor in the cell membrane, adenylate cyclase is activated and the second messenger, cyclic AMP is formed. The adrenergic receptor is closely linked to the insoluble membrane bound enzyme, probably by a phospholipid. Cyclic AMP is then bound to protein kinase which in turn, usually by phosphorylation, activates other enzymes which carry out the function of the cell. In the case of glycogenolysis these steps have been quite well worked out. For most other adrenergic functions the steps subsequent to formation of cyclic AMP remain fairly conjectural (Reed, 1978).

The studies by Lands and his coworkers in the mid 1960's gave a chemical explanation for apparent alpha, beta-1 or beta-2 adrenergic selectivity of various catecholamine analogues. This stimulated the appearance of a flood of catecholamine and resorcinol derivatives in order to find one with complete beta-2 specificity.

Taking epinephrine (Fig. 1) as a prototype catecholamine through various modifications of the constituents and their locations on the basic catecholamine ring, agents with prolong duration of action have been produced. This increased duration is presumably due

to the lack of degradation by catechol-0-methyl transferase (COMT). This enzyme substitutes a methyl group for the hydrogen which is present on the meta-hydroxyl group of the catechol ring. Primarily through enlargement of the moiety attached to the nitrogen end of the catecholamine, agents with greater beta-2 specificity have been produced. The "keyhole" theory of beta adrenergic receptors states that the more bulky the nitrogen-attached moiety on a catechol or resorcinol base, the more beta-2 specific the agent. The smaller the nitrogen-attached moiety, the more the activity shifts to non-specific alpha and beta stimulation, until we reach a total absence of a nitrogen-attached moiety, as in norepinephrine (Fig. 1), with only alpha activity.

Fenoterol, a bronchodilator drug, has been used in asthma for more than 15 years ago. It has the resorcinol derivative structure. As seen in Fig. 1, this agent has an extremely large moiety attached to the terminal nitrogen which makes it a large "key", so it is highly beta-2 specific. Since fenoterol has hydroxyl groups on the 3,5 positions of the benzene ring, it was reported not to be metabolized by COMT (Persson and Olsson, 1970). Metabolism by MAO is not likely to occur to any degree since a large substituent on the nitrogen makes the molecule resistant to MAO (Giles et al, 1973).

The pharmacokinetics of fenoterol was investigated using tritium-labelled compound and the appropriate isotope technics in rats, dogs and humans (Rominger, 1970; Buchelt, 1970). The biological half-life of fenoterol after i.v. administration in the dogs and rats is approximately 2-2½ hours. As shown by the intravenous

blood level, fenoterol is very rapidly taken up by the tissues. Tissue level determinations and autoradiography in the rats show that no appreciable accumulations are produced by uptake of fenoterol in any organs apart from the excretory organs, in particular the kidneys and to a certain extent the liver. Because of the high renal excretion rate, very high concentrations are reached for a short period in the kidneys, but these fall again very rapidly with urine excretion.

After oral administration, renal excretion in rats amounts to 15% of the administered dose, whereas in dog 70% of the administered dose is excreted via the kidneys, and in man 39%.

The blood level in dogs reaches a maximum only 30 min. to one hour after oral administration; in man the blood level maximum occurs later, between one and two hours after administration. The biological half-life of fenoterol in rats and dogs are 2-2½ hours and 7 hours in man.

While in rats and dogs, considerable quantities of fenoterol are detectable in the urine after oral administration, in man less than 2% unchanged active ingredient is excreted. The main fraction of renal excretion products are acid conjugates, the mixture of glucoronides and sulphates.

Investigation of the pharmacokinetic behavior of these substances after oral or intravenous administration is not particularly problematical, whereas pharmacokinetic investigations following aerosol administration present problems which research science has so far

been unable to solve satisfactorily. Since the particle size of the aerosol used at any particular moment is not known, thus it is impossible to make any statements on the site of deposition of particles (Laros et al, 1975).

In this study, the experiments were done up to 8 hours which was long enough to follow the effects of fenoterol aerosols since the biological half-life of fenoterol was 7 hours in man (Rominger, 1970: Buchelt, 1970).

Recent reports have demonstrated that fenoterol was a long-acting, relatively selective bronchodilator. Beardshaw et al (1974) compared aerosolized doses of fenoterol and metaproterenol and found that fenoterol produced bronchodilation lasting over 3 hours following a dose of 400 micrograms; no definite advantage was found when the drug was administered in a dose of 800 micrograms. Benjamin, 1972 reported that significant bronchodilation lasted up to the 5th hour following use of 400 micrograms aerosolized fenoterol.

Emergril et al (1977) demonstrated that fenoterol aerosols had an onset of action which was just as rapid as isoproterenol and a duration of action that was markedly superior. Side effects were minimal and did not occur with any greater frequency with fenoterol than with isoproterenol.

Another study (Ruffin et al, 1978) has shown that 500 micrograms of fenoterol administered to the buccal mucosa had no significant bronchodilator effect compared to smaller inhaled dose of

fenoterol. In fact, some investigators assumed that more than 90% of the dose from a metered-dose inhaler was deposited in the mouth and that some of this was swallowed and absorbed by the intestinal tract (Davies, 1972). This assumption was supported by recent pharmacokinetic data. The work of Laros et al (1977) demonstrated that the course of the plasma level after aerosol administration is indistinguishable from that after oral administration.

It was clear that fenoterol increased mucous transport in airways by increasing ciliary beating frequency and possibly by altering the quantity and character of the mucous secretions. Yeates et al (1976) suggested that bronchodilation induced by the adrenergic agonists did not appear to increase mucociliary clearance by changing the circumference of the epithelial surface of the airways.

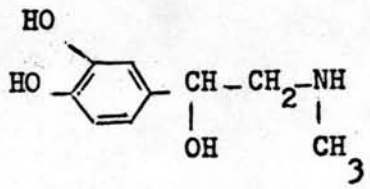
Ruffin et al (1978) demonstrated that inhalation of 200 micrograms of fenoterol from a metered-dose inhaler was as effective as 400 micrograms in producing bronchodilation. It was found that aerosol fenoterol completely blocked post-exercise bronchoconstriction immediately after inhalation and for up to four hours in asthmatic subjects. It may be postulated that there were two sites of action of a beta adrenergic stimulant, one in the bronchial smooth mucle and the other more superficially placed in or on the surface of the bronchial mucosa (perhaps the mast cell). Stimulation of the former by beta adrenergic drugs resulted in a relaxation of the smooth muscle whilst the action of these drugs on the latter receptor is to block exercise-induced bronchoconstriction. So it was suggested that the superiority

of the aerosol in blocking exercise-induced bronchoconstriction may be a function of its activity at the surface of the bronchial mucosa (Anderson et al, 1975).

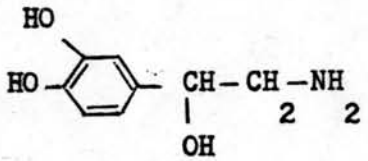
In this study, symptomatic asthmatic patients were selected. It differed from other experiments which used histamine-induced asthmatic patients (Beumer, 1971) or patients known to show at least 15% improvement in their FEV_1 with challenging isoproterenol (Lal et al, 1974).

Figure 1. Chemical structure of important sympathomimetic drugs.

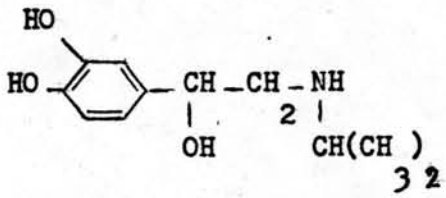
Epinephrine



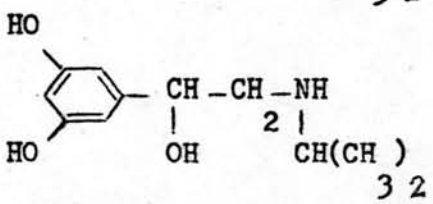
Norepinephrine



Isoproterenol



Metaproterenol



Fenoterol