A STUDY OF EFFICACY AND SAFETY OF ORAL AMINOPHYLLINE COMPARED TO DOXOFYLLINE IN CHRONIC BRONCHIAL ASTHMA

DISSERTATION SUBMITTED TO

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IN PARTIAL FULFILLMENT

OF THE REQUIREMENT FOR THE DEGREE OF

M.D IN **PHARMACOLOGY**

By

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UNDER THE GUIDANCE OF

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APRIL– 2011

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LIST OF ABBREVATIONS

AHR- Airway hyperresponsiveness

cAMP- cyclic Adenosine Mono Phosphate

COPD- Chronic Obstructive Pulmonary Disease

ERV - Expiratory Reserve Volume

$FEF_{25-75\%}$ - Forced Mid Expiratory Flow

FEV_1- Forced Expiratory Volume in 1 s

FRC - Functional Residual Capacity

FVC- Forced Vital Capacity

IC - Inspiratory Capacity

IRV - Inspiratory Reserve Volume

LK- Leukotrienes

MDIs- Metered Dose Inhalers

MMEF- Mid- Maximal Expiratory Flow

PDE- Phosphodiesterase

PEFR- Peak Expiratory Flow Rate

PFT- Pulmonary function Test

RAST- Radioallergosorbent tests

RSV- Respiratory Syncytial Virus

RV - Residual Volume

TLC - Total Lung Capacity

TNF- Tumor Necrosis Factor

TV - Tidal Volume

VC - Vital Capacity

ABSTRACT

Background/Objectives:

To compare the clinical efficacy and safety of oral Aminophylline and Doxofylline in the treatment of chronic bronchial asthma

Materials and Methods:

Relevant data were taken from patients with chronic bronchial asthma with mild to moderate severity, presenting to the Department of Medicine at R.L.Jalappa Hospital and research centre from December 2008 to May 2010. A total of 60 patients were enrolled in the study. They were randomized into two groups of 30 each. Patients in the first group received oral aminophylline 225mg while those in the second group were given oral doxofylline 400 mg following baseline pulmonary function test (PFT). Post medication PFT was done 4hrs after drug administration and Spirometric response was assessed. Changes in Heart rate, Blood Pressure and respiratory rate were also assessed. Adverse effects of both the drugs were recorded.

Laboratory tests included chest x-ray and ECG as and when appropriately needed.

Results:

When pulmonary function test parameters between the groups were compared, a significant improvement was observed in the Doxofylline group in FEV_1 (0.001), FVC (0.009), $FEF_{25-75\%}$ (p 0.029) percentage predicted value. Both the treatments showed significant improvement in FEV_1, PEFR. Doxofylline treated patients also showed improvement in FVC and $FEF_{25-75\%}$.

Adverse events were reported in both the groups but were mild in nature. Headache, nausea and heart burn were reported more in aminophylline treated group compared to doxofylline group.

Conclusion:

The results of the present study show that administration of oral Doxofylline 400mg single dose is more effective and safe than sustained release Aminophylline 225 mg tablet.

Keywords: Asthma; Pulmonary Function Test; Aminophylline; Doxofylline.

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INTRODUCTION

Asthma is one of the few chronic diseases that have shown consistently upward trend through the last few decades. Highly effective drugs are now available for the management of asthma that has led to a marked reduction in hospital admissions and mortality. The advances in asthma therapy have been largely through improving the selectivity and duration of action of existing effective classes of drugs. With respect to this, pharmacology has played an important role in validating drug targets and drug design.

The most effective treatments for asthma are β_2-adrenoceptor agonists and corticosteroids.[1] Methylxanthine are still widely used in the treatment of asthma. Being one of the few drugs that can be administered orally they are helpful in resource restricted settings.[2] Aminophylline, a methylxanthine, indicated for the treatment of Asthma and Chronic Obstructive Pulmonary Disease (COPD) and remains one of the most widely prescribed drugs for the treatment of obstructive airway diseases.[3] Doxofylline is a novel drug which shares most of the characteristics of the methylxanthine drugs, is associated with less extra respiratory effects than Theophylline. Even at the highest recommended dose, Doxofylline is better tolerated than Theophylline.[4]

Since slow release oral Aminophylline is used commonly and Doxofylline has emerged recently as a promising drug, the present study has been taken up to compare the efficacy and safety profile of oral Aminophylline and Doxofylline.

AIMS AND OBJECTIVES

1. To compare the clinical efficacy of slow release oral Aminophylline and Doxofylline in the treatment of chronic bronchial asthma.

2. To compare the safety of slow release oral Aminophylline and Doxofylline in the treatment of chronic bronchial asthma.

REVIEW OF LITERATURE

DEFINITION:

Asthma is a chronic inflammatory disorder of the airways that causes recurrent episodes of wheezing, breathlessness, chest tightness, and cough, particularly at night and /or in the early morning. These symptoms are usually associated with widespread but variable bronchoconstriction and airflow limitation that is at least partly reversible, either spontaneously or with treatment. The hallmarks of the disease are: increased airway responsiveness to a variety of stimuli, resulting in episodic bronchoconstriction; inflammation of the bronchial walls; and increased mucus secretion. Some of the stimuli that trigger attacks in patients would have little or no effect in subjects with normal airways.[5]

HISTORY OF BRONCHIAL ASTHMA:

Ephedra, known to the inhabitants of China for more than five thousand years as mahuang, is a remedy whose medicinal benefits were recognized and employed for millennia before its pharmacological properties were characterized. Ephedrine, the active ingredient in ephedra, relieves bronchospasm, produces vasoconstriction, reverses congestion, and inhibits mucus secretion. The Chinese brought ephedra to Greece from where it was introduced to other civilizations. The Ebers Papyrus and other medical works by early Egyptian authors described a sophisticated approach to the practice of medicine. Asthma was considered to be a whdw (disorder or foulness) of the metu (ducts that were thought to distribute air and water to the organs, including the lungs). The Ebers papyrus also recommended the use of a special apparatus for inhalation in cases of restricted breathing. Hippocrates the 'Father of Medicine' described 'panting', which he termed asthma. The actual term asthma is a

Greek word that is derived from the verb aazein, meaning to exhale with open mouth, 'to pant'. The British army, following its nineteenth century incursion into India, introduced to the West, the practice of smoking stramonium as a treatment for asthma-substituting the temperate genus Datura stramonii for the tropical genus Datura ferox. Maimonides (1135.1204) suggested comprehensive treatment measures, including rest, good personal hygiene, environmental hygiene, equanimity, and avoidance of opium and also focused on the effects of diet on health.[6] Asthma has long been considered a psychosomatic disease, and during the 1930s–50s, was even known as one of the 'holy seven' psychosomatic illnesses. At that time, psychoanalytic theories described the etiology of asthma as psychological, with treatment often primarily involving psychoanalysis and other 'talking cures'.[7] Anti-asthma cigarettes have virtually disappeared, though the therapeutic principles of the smoking cure have not been entirely eclipsed. At the start of the twenty-first century, inhaled treatments continue to dominate the management of asthma.[8]

EPIDEMIOLOGY:

The epidemiology of asthma is an area of research that is complex and essential to enhancing the understanding of a disease that has a significant impact on the morbidity and mortality of a large number of patients. The challenges faced by epidemiologists who study asthma begin with the lack of a universal definition for the disease that is pathophysiologically and clinically applicable. Asthma was first defined by the American Thoracic Society in 1962 as a disease characterized by increased responsiveness of the trachea and bronchi to various stimuli and manifested by widespread narrowing of the airways that changes in severity either spontaneously or as a result of therapy.[9]

Prevalence - Asthma is one of the most common chronic diseases globally and currently affects ~300 million people. The prevalence of asthma has risen in affluent countries over the last 30 years but now appears to have stabilized, with ~10–12% of adults and 15% of children affected by the disease. In developing countries where the prevalence of asthma had been much lower, there is a rising incidence that appears to be associated with increased urbanization.[10] Asthma can occur at any age. However, in half the cases, the onset is before 10 years of age. Asthma is thought to affect about 3% of the population in most countries. The highest prevalence (almost 30%) is found in New Zealand. The prevalence in a number of countries falls in the range 10%–17%.[11]

According to the National Family Health Survey-2 report, the estimated prevalence of asthma in India is 2468 per 100,000 persons. The prevalence was higher in rural than in urban areas (2649 *v.* 1966). The prevalence among males was slightly higher (2561) than among females (2369). Among those below 15 years of age, asthma was seen in 950 per 100,000 persons. The prevalence rate was 2309 among those in the age group of 15–59 years, while it was 10,375 in those above 60 years of age. The prevalence of asthma in adult males (18 years and above) during 1995–97 was 3.94% in urban and 3.99% in rural areas.[12]

ETIOLOGY:

Asthma may be categorized into atopic (evidence of allergen sensitization, often in a patient with a history of allergic rhinitis, eczema) and non-atopic (without evidence of allergen sensitization). In either type, episodes of bronchospasm can be triggered by diverse mechanisms, such as respiratory infections (especially rhinovirus, respiratory syncytial virus, and coronavirus infections), environmental exposure to irritants (e.g., smoke, fumes), cold air, stress, and exercise. Recent studies have suggested that

the recognition of sub-phenotypes of asthma based on the pattern of airway inflammation may also be useful. There is emerging evidence for differing patterns of airway inflammation: eosinophilic, neutrophilic, mixed inflammatory and pauci-granulocytic asthma. These subgroups may differ in their etiology, immunopathology, and response to treatment.[13]

Atopic asthma - This most common type of asthma is a classic example of type I IgE – mediated hypersensitivity reaction. The disease usually begins in childhood and is triggered by environmental allergens, such as dusts, pollens, roach or animal dander, and foods. A positive family history of asthma is common, and a skin test with the offending antigen in these patients results in an immediate wheal-and-flare reaction. Atopic asthma may also be diagnosed based on evidence of allergen sensitization by serum radioallergosorbent tests (called RAST), which identify the presence of IgE specific for a panel of allergens.

Non-Atopic Asthma- The second group of individuals with asthma does not have evidence of allergen sensitization, and skin test results are usually negative. A positive family history of asthma is less common in these patients. Respiratory infections due to viruses (e.g., rhinovirus, parainfluenza virus) are common triggers in non-atopic asthma.[14]

Drug Induced Asthma- Aspirin-sensitive asthma is an uncommon yet fascinating type, occurring in individuals with recurrent rhinitis and nasal polyps. These individuals are exquisitely sensitive to small doses of aspirin as well as other nonsteroidal anti-inflammatory medications, and they experience not only asthmatic attacks but also urticaria. It is probable that aspirin triggers asthma in these patients by inhibiting the cyclooxygenase pathway of arachidonic acid metabolism without

affecting the lipooxygenase route, thus tipping the balance and leading to elaboration of the bronchoconstriction leukotrienes.[15]

Infections- Viral respiratory infections are important in both the pathogenicity of asthma and in the induction of asthma exacerbations. Most viral infections are secondary to rhinoviruses. Long term prospective studies have demonstrated that Respiratory syncytial virus (RSV) infections are an independent risk factor for future wheezing in the first 10 years of life. Non- RSV lower airway viral infections during infancy and early childhood may be associated with the development of asthma. A new paradigm in asthma pathogenesis is being entertained: that, bacterial infections in particular Mycoplasma pneumoniae and Chlamydia pneumoniae are involved in the pathobiology of both chronic and acute asthma.[16]

Environmental factors

Allergens- Studies to evaluate house-dust mite and cockroach exposure have shown that the prevalence of sensitization and subsequent development of asthma are linked. Exposure to cockroach allergen, for example, a major allergen in inner-city dwellings, is an important cause of allergen sensitization, a risk factor for the development of asthma.[17]

Air pollution-The role of air pollution in the development of asthma remains controversial and may be related to allergic sensitization.[18]

Obesity-Increasing rates of obesity have paralleled increasing rates in asthma prevalence, but the interrelation is uncertain. Obesity may be a risk factor for asthma due to the generation of unique inflammatory mediators that lead to airway dysfunction.[19]

In utero exposure to environmental tobacco smoke increases the likelihood for wheezing in the infant, although the subsequent development of asthma has not been well defined. In adults who have asthma, cigarette smoking has been associated with an increase in asthma severity and decreased responsiveness to inhaled corticosteroids.[20]

NEUROLOGIC CONTROL OF ASTHMA:

Because asthma involves dysfunction in the pathways that regulate both smooth muscle tone and immune function in the airways, it is important to know the normal physiology. In the airways, sympathetic (adrenergic) tone causes bronchodilation and parasympathetic (cholinergic) tone causes bronchoconstriction. Adrenergic receptors mediate sympathetic innervations of the lungs. Airway smooth muscle cells express β_2-adrenergic receptors. The vagus nerve provides parasympathetic innervations to the lungs. Airway smooth muscle cells express muscarinic receptors, especially the excitatory M_3 subtype of muscarinic receptors. Upon stimulation by acetylcholine released by parasympathetic postganglionic neurons, these receptors induce bronchoconstriction. Parasympathetic neurons are dominant in maintaining smooth muscle tone, and anticholinergic agents can cause bronchorelaxation.[21]

GENETICS IN ASTHMA:

Asthma is a complex genetic trait in which multiple susceptibility genes interact with environmental factors to initiate the pathological reaction. Some genes may influence the development of asthma, while others modify asthma severity or the patient's response to therapy.[22]

One of the replicated susceptibility loci for asthma is on chromosome 5q, near the gene cluster encoding the cytokines IL-3, IL-4, IL-5, IL-9, and IL-13 and the IL-4 receptor. The receptor for LPS (CD14), and another candidate gene, the β_2-adrenergic receptor, also map here. Polymorphisms in the IL-13 gene have the strongest and most consistent associations with asthma or allergic disease. In some studies, the TT genotype of CD 14 has been associated with reduced levels of IgE and reduced risk for asthma and atopy. Other studies have revealed the opposite, i.e., an increased risk of atopy. Further analysis has revealed that the TT genotype is protective against asthma or allergic sensitization in individuals exposed to low endotoxin levels, whereas the same genotype is associated with an increased risk for asthma or allergic sensitization in individuals exposed to high endotoxin levels. These differences may relate to the influence of endotoxin levels on the regulation of T_H1 v/s T_H 2 responses.[23, 24]

ADAM-33: ADAM-33 belongs to a subfamily of metalloproteinases related to collagenases. Although the precise function of ADAM-33 remains to be elucidated, it is known to be expressed by lung fibroblasts and bronchial smooth muscle cells. It is speculated that ADAM-33 polymorphisms accelerate proliferation of bronchial smooth muscle cells and fibroblasts, thus contributing to bronchial hyperreactivity and subepithelial fibrosis.[25]

A number of single nucleotide polymorphisms have been identified within the coding region of the gene[26], with only four resulting in amino acids changes. These occur at codons 16, 27, 34, and 164 and have been studied extensively. The polymorphism at position 164 affects the binding region for β_2-agonists by disrupting receptor coupling to G proteins, decreasing binding. Polymorphisms at codon 34 have not been shown to have any functional significance. The polymorphisms at position 16 and 27 have

been associated with increased down-regulation of the receptors, loss of receptor number, and a reduced clinical response.[27]

IL-4 receptor gene: Multiple polymorphic variants in the gene encoding the alpha-chain of the IL-4 receptor are associated with atopy, elevated total serum IgE, and asthma.

Mammalian chitinase family: Chitinases are enzymes that cleave chitin, a polysaccharide contained in many human parasites and the cell walls of fungi. In humans chitinase family includes members with or without enzymatic activity. One member with activity, acidic mammalian chitinase, is up-regulated in and contributes to T_H 2 inflammation. Another chitinase family member with no enzymatic activity, YKL-40, is associated with asthma. Serum levels of YKL-40 correlate with the severity of asthma.[28]

PATHOGENESIS:

The major etiologic factors in atopic asthma are a genetic predisposition to type I hypersensitivity ("atopy") and exposure to environmental triggers that remain poorly defined.[29]It is postulated that inheritance of susceptibility genes makes individuals prone to develop strong T_H2 reactions against environmental antigens (allergens) that are ignored or elicit harmless responses in most individuals. In the airways the scene for the reaction is set by initial sensitization to inhaled allergens, which stimulate induction of T_H2 cells. T_H2 cells secrete cytokines that promote allergic inflammation and stimulate B cells to produce IgE and other antibodies. These cytokines includes IL-4 which stimulates the production of IgE; IL-5 which activates locally recruited eosinophils; and IL-13 which stimulates mucus secretion from bronchial submucosal glands and also promotes IgE production by B cells. As in other allergic reactions, IgE coats submucosal mast cells to release granule contents and produce cytokines

and other mediators, which collectively induce the early- phase (immediate hypersensitivity) reaction and the late-phase reaction.

The early- reaction dominated by bronchoconstriction, increased mucus production and variable degrees of vasodilatation with increased vascular permeability. Bronchoconstriction is triggered by direct stimulation of subepithelial vagal (parasympathetic) receptors through both central and local reflexes (including those mediated by unmyelinated sensory C fibers).

The late- phase reaction consists largely of inflammation with recruitment of leukocytes, notably eosinophils, neutrophils, and more T cells. Leukocyte recruitment is stimulated by chemokines produced by mast cells, and by other cytokines.

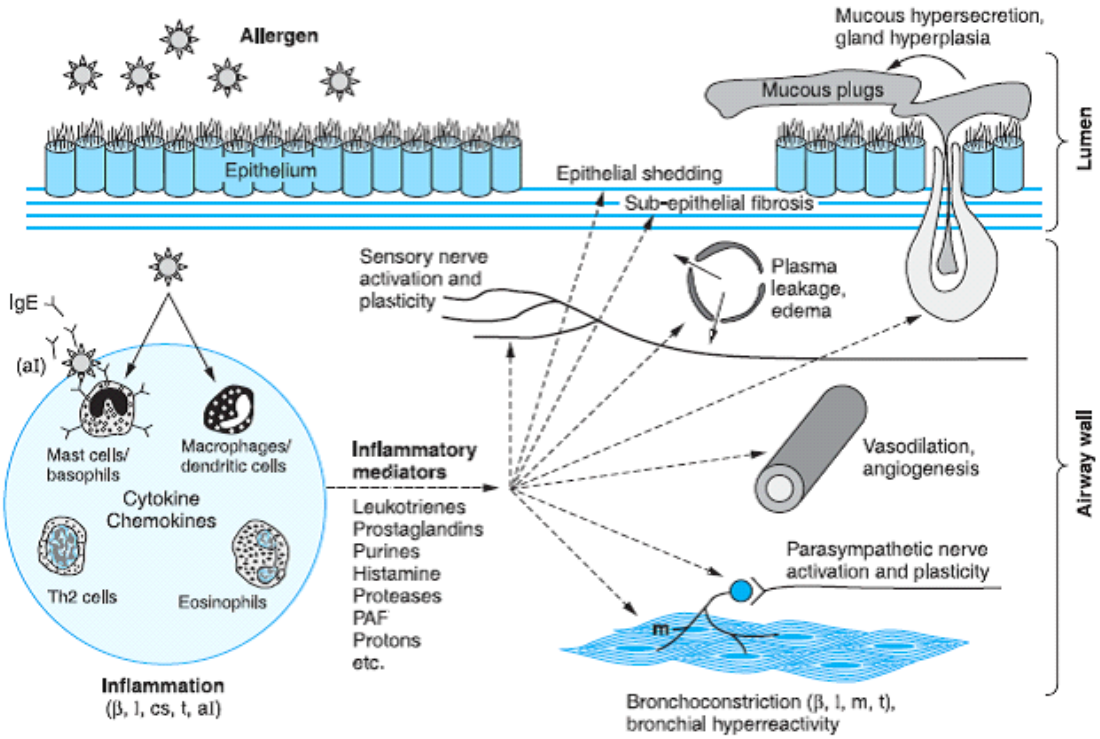


FIGURE 1: Pathogenesis

Epithelial cells are known to produce a large variety of cytokines in response to infectious agents, drugs, and gases as well as to inflammatory mediators.[30]This second wave of mediators stimulate the late reaction. For example, eotoxin, produced by airway epithelial cells, is a potent chemo attractant and activator of eosiniphils.[31] The major basic protein of eosinophils, in turn, causes epithelial damage[30] and more airway constriction.[32] Many mediators have been implicated in the asthmatic response, but the relative importance of each putative mediator in actual human has been difficult to establish. The long list of "suspects" in acute asthma can be subclassified by the clinical efficacy of pharmacological intervention with inhibitors or antagonists of the mediators.

The first group includes putative mediators whose role in bronchospasm is clearly supported by efficacy of pharmacological interventions

- Leukotrienes C_4, D_4, and E_4, extremely potent mediators that cause prolonged bronchoconstriction as well as increased vascular permeability and increased mucus secretion.
- Acetylcholine, released from motor nerves, which can cause airway smooth muscle constriction by directly stimulating muscarinic receptors.

A second group includes agents present at the scene of the crime and with potent asthma- like effects but whose actual role in acute allergic asthma seems relatively minor on the basis of lack of efficacy of potent antagonists or synthesis inhibitors;

- Histamine, a potent bronchoconstrictor.
- Prostaglandin D_2, which elicits bronchoconstriction and vasodilatation; and
- Platelet –activating factor, which causes aggregation of platelets and release of histamine and serotonin from their granules.

Finally, a large third group comprises the suspects for whom specific antagonists or inhibitors are not available or have been insufficiently studied yet. These include numerous cytokines, such as IL-I, TNF, and IL-6.[33]

Over time, repeated bouts of allergen exposure and immune reactions result in structural changes in the bronchial wall, referred to as "airways remodeling."These changes include hypertrophy and hyperplasia of bronchial smooth muscle, epithelial injury, increased airway vascularity, increased subepithelial mucus gland hypertrophy/ hyperplasia, and deposition of subepithelial collagen.[15]

MORPHOLOGY:

The most striking macroscopic finding is occlusion of bronchi and bronchioles by thick, tenacious mucus plugs.

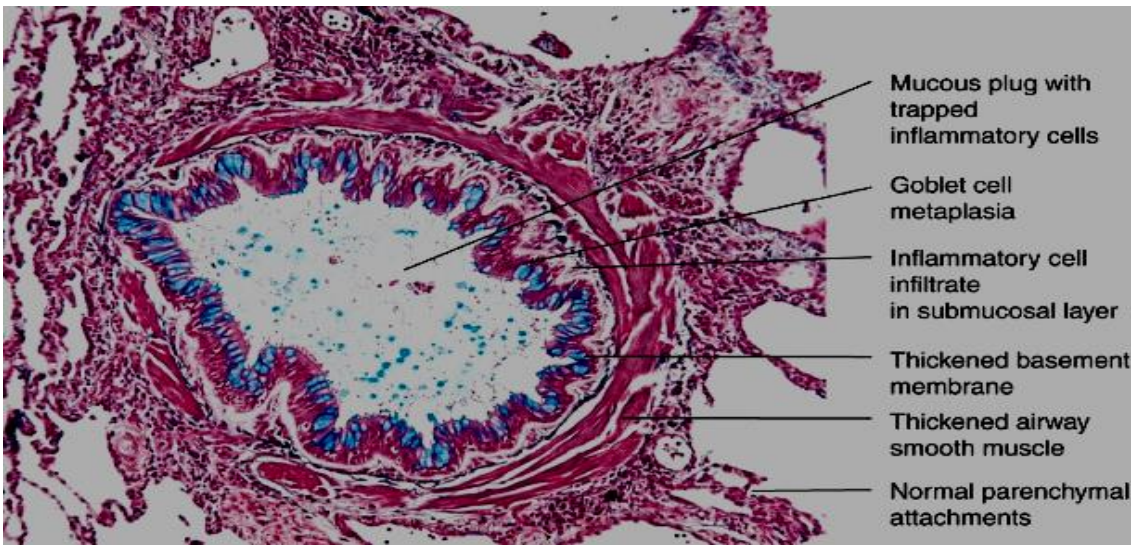


FIGURE 2: Histology

Histologically, the mucus plugs contain whorls of shed epithelium, which give rise to the well known spiral shaped mucus plugs called Curschmann spirals. Numerous eosiniphils and Charcot-Leydon crystals are present; the latter are collection of

crystalloid made up of an eosinophil lysophospholipase binding protein called galectin-10.[34]

The other characteristic histological findings of asthma, collectively called "airway remodeling" include,

- Overall thickening of airway wall
- Sub-basement membrane fibrosis (due to deposition of type I and III collagen beneath the classic basement membrane composed of type IV collagen and laminin)
- Increased vascularity.
- An increase in size of the submucosal glands and mucous metaplasia of airway epithelial cells.
- Hypertrophy and/or hyperplasia of the bronchial wall muscle.[35]

PATHOPHYSIOLOGY:

Limitation of airflow is due mainly to bronchoconstriction, but airway edema, vascular congestion, and luminal occlusion with exudate may also contribute. This results in a reduction in forced expiratory volume in 1 s (FEV_1), FEV_1/forced vital capacity (FVC) ratio, and peak expiratory flow (PEF), as well as an increase in airway resistance. Early closure of peripheral airway results in lung hyperinflation (air trapping), and increased residual volume, particularly during acute exacerbations. In more severe asthma, reduced ventilation and increased pulmonary blood flow result in mismatching of ventilation and perfusion and in bronchial hyperemia. Ventilatory failure is very uncommon, even in patients with severe asthma, and arterial Pa_{CO2} tends to be low due to increased ventilation.

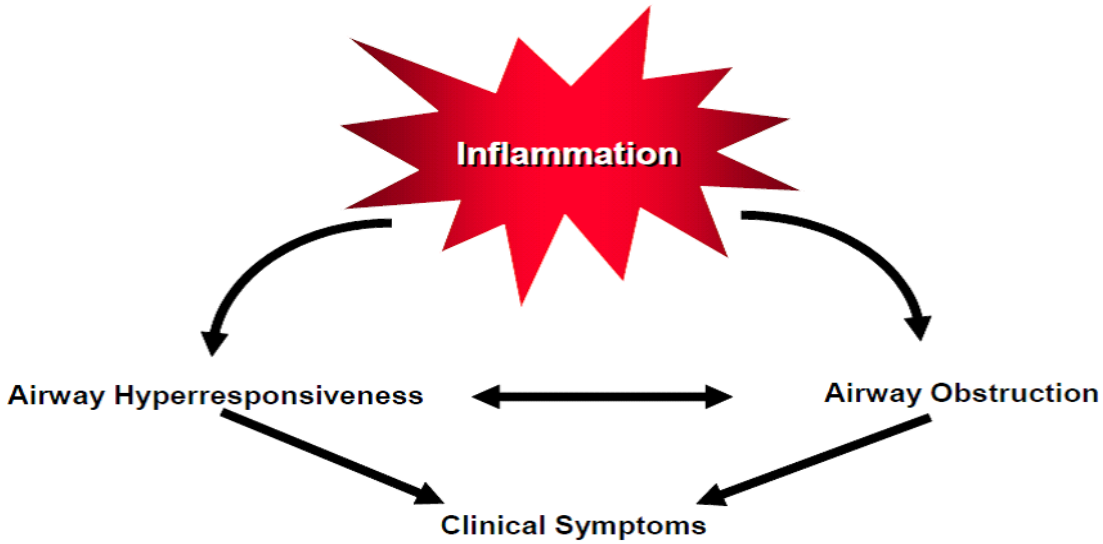


FIGURE 3: Airway hyperresponsiveness

Airway hyperresponsiveness-AHR is the characteristic physiologic abnormality of asthma, and describes the excessive bronchoconstrictor response to multiple inhaled triggers that would have no effect on normal airways. The increase in AHR is linked to the frequency of asthma symptoms; thus, an important aim of therapy is to reduce AHR. Increased bronchoconstrictor responsiveness is seen with direct bronchoconstrictors, such as histamine and methacholine, which contract airway smooth muscle, but it is characteristically also seen with many indirect stimuli, which release bronchoconstrictors from mast cells or activate sensory neural reflexes. Most of the triggers for asthma symptoms appear to act indirectly, including allergens, exercise, hyperventilation, fog (via mast cell activation), irritant dusts, and sulfur dioxide (via cholinergic reflex).[10]

CLINICAL FEATURES:

Asthma course is usually one with periods of normality punctuated by attacks of cough, wheeze and breathlessness. Asthma is revoked by exercise, allergens, viral illness and change in temperature with marked diurnal variability. Episodic expiratory

wheeze, cough, and as severity increases, there will be increase in breathlessness, chest tightness culminating in difficulty in talking and cyanosis during a severe attack. Characteristic clinical findings are wheeze, usually polyphonic and in severe cases, tachycardia and pulsus paradox. Ability to talk, pulse rate, and arterial blood gas provide the best indicators of severity.[36]

DIAGNOSIS:

The diagnosis of asthma is usually apparent from the symptoms of variable and intermittent airways obstruction, but is usually confirmed by objective measurements of lung function.

Lung Function Tests

Simple spirometry confirms airflow limitation with a reduced Forced Expiratory Volume in 1st second (FEV_1), FEV_1/FVC ratio (FVC-Forced Vital Capacity), and Peak Expiratory Flow (PEF). Reversibility is demonstrated by a >12% or 200 mL increase in FEV_1, 15 min after an inhaled short-acting β_2-agonist or, in some patients, by a 2- to 4-week trial of oral glucocorticoids (prednisone or prednisolone 30–40 mg daily). Measurements of PEF twice daily may confirm the diurnal variations in airflow obstruction. Flow-volume loops show reduced peak flow and reduced maximum expiratory flow. Further lung function tests are rarely necessary, but whole body plethysmography shows increased airway resistance and may show increased total lung capacity and residual volume. Gas diffusion is usually normal but there may be a small increase in gas transfer in some patients.

Airway Responsiveness

The increased AHR is normally measured by methacholine or histamine challenge with calculation of the provocative concentration that reduces FEV_1 by 20% (PC_{20}).

This is rarely useful in clinical practice, but can be used in the differential diagnosis of chronic cough and when the diagnosis is in doubt in the setting of normal pulmonary function tests. Occasionally exercise testing is done to demonstrate the post-exercise bronchoconstriction if there is a predominant history of exercise induced asthma. Allergen challenge is rarely necessary, and should only be undertaken by a specialist if specific occupational agents are to be identified.

Hematologic Tests

Blood tests are not usually helpful. Total serum IgE and specific IgE to inhaled allergens (RAST) may be measured in some patients.

Imaging

Chest roentgenography is usually normal but may show hyperinflated lungs in more severe patients. In exacerbations, there may be evidence of a pneumothorax. Lung shadowing usually indicates pneumonia or eosinophilic infiltrates in patients with bronchopulmonary aspergillosis. High-resolution Computerized Tomography may show areas of bronchiectasis in patients with severe asthma, and there may be thickening of the bronchial walls, but these changes are not diagnostic of asthma.

Skin Tests

Skin prick tests to common inhalant allergens are positive in allergic asthma and negative in intrinsic asthma, but are not helpful in diagnosis. Positive skin responses may be useful in persuading patients to undertake allergen avoidance measures.[10]

TABLE 1 Grading of bronchial asthma

Step	Status	Symptoms	Lung Function (FEV_1)
1.	Mild intermittent	≤ Twice a week	≥ 80% predicted
2.	Mild persistent	> Twice a week but < once a day. Exacerbations may affect activity	≥ 80% predicted
3.	Moderate persistent	Daily Daily use of β_2- agonists Exacerbations may affect activity Exacerbations ≥twice a week	60–80% predicted
4.	Severe persistent	Continual symptoms Limited physical activity Frequent exacerbations	≤ 60%.[37]

DIFFERENTIAL DIAGNOSIS:

Diseases causing recurrent episodic dyspnea- Chronic obstructive pulmonary disease, Coronary artery disease, congestive heart failure, pulmonary emboli, recurrent gastroesophageal reflux with aspiration.

Common diseases causing cough - Rhinitis, sinusitis, otitis, bronchitis, cystic fibrosis.

Common diseases causing airflow obstruction – Chronic obstructive bronchitis and emphysema, bronchitis obliterens, organic or functional laryngeal narrowing.[38]

PRINCIPLES OF THERAPY:

Drug therapy is preferably given by inhalation to deliver the drugs directly to the desired site of action. This produces higher local concentrations and permits smaller doses than would be required orally, with a consequent reduction in adverse effects. Systematic reviews have found that hand-held inhaler devices including pressurized metered dose inhalers (MDIs), dry powder inhalers, and breath actuated pressurized MDIs, are generally equally effective for the delivery of short-acting β_2-agonists and corticosteroids in stable asthma. Spacer devices can be fitted to some MDIs to act as reservoirs for the drug to make it easier for the patient to inhale each dose correctly. Use of MDIs with spacer devices produces outcomes which are at least equivalent to nebulizer therapy. Nebulizers tend to be reserved for patients who are unable or unwilling to use these devices, although the choice of spacer and method of use may substantially affect drug delivery.[39]

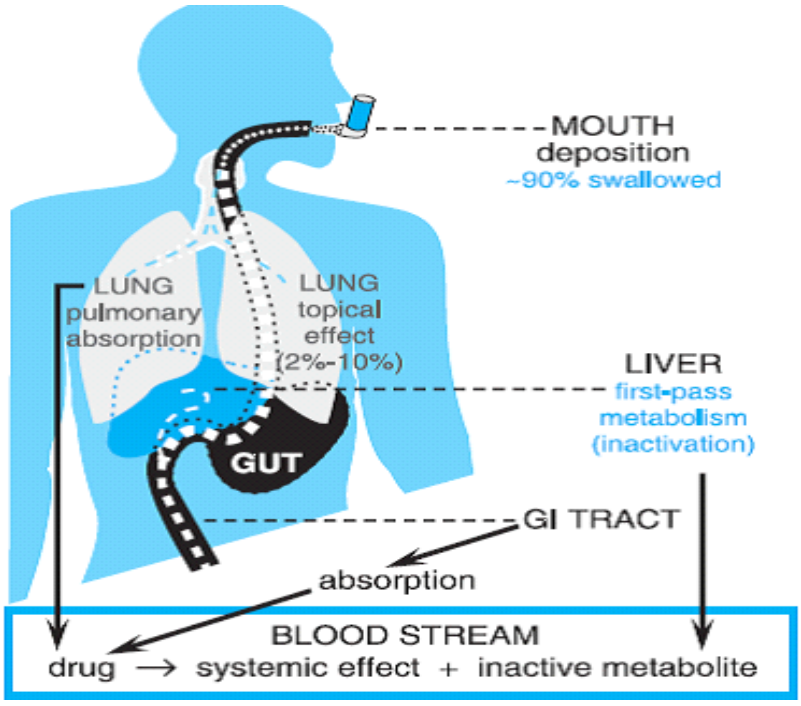


FIGURE 4: Pharmacokinetics of aerosolized drug

Even under ideal circumstances, only a small fraction of the aerosolized drug is deposited in the lungs, typically 2–10%. Most of the remainder is swallowed. To minimize systemic effects, an aerosolized drug should be either poorly absorbed from the gastrointestinal system or rapidly inactivated via first-pass hepatic metabolism as in figure 4. Because >50% of patients using inhalers do not use proper technique and thus deposit too small a fraction of inhaled drug into the lungs, patients should be counseled in the proper use of an inhaler.[2]

The main drugs for asthma can be divided into bronchodilators, which give rapid relief from symptoms mainly through relaxation of airway smooth muscle, and controllers, which inhibit the underlying inflammatory process.

BRONCHODILATOR THERAPIES:

Bronchodilators act primarily on airway smooth muscle to reverse the bronchoconstriction of asthma. This gives rapid relief of symptoms but has little or no effect on the underlying inflammatory process. There are three classes of bronchodilator in current use: β_2-adrenergic agonists, anticholinergics and methylxanthines.[10]

β_2 –ADRENERGIC AGONISTS

β_2 -Adrenergic agonists are potent bronchodilators. Two classes of β_2-Adrenergic agonists exist: Short acting (albuterol, levalbuterol, the (R)-enantiomer of albuterol metaproterenol, terbutaline, and pirbuterol) and long-Acting (salmeterol xinafoate and formoterol). Adrenergic receptors belong to the G-protein-linked rhodopsin-related receptor super families. When a β_2-Adrenergic agonist binds to the receptor on the cell membrane, GDP is released from G protein, which is a membrane-associated heterotrimer. This enables GTP to bind to the β-receptor, which activates adenylyl cyclase, catalyzing formation of cyclic cAMP. Cytosolic calcium ion concentration

decreases and smooth muscle relaxation ensues. Other mechanisms of smooth muscle relaxation include shifting of myosin light-chain kinase to a less active form, cAMP inhibition of phospholipase C and reduction of 1,4,5-triphosphate formation, stimulation of a calcium –activated potassium channels, and inhibition of acetylcholine release from cholinergic neurons.[40] β_2 -Adrenergic agonists may be given orally, or by inhalation. Inhalation provides a more rapid onset of action and fewer side effects. β_2 -Adrenergic agonists also can be administered intravenously in patients with impending respiratory failure, but potentially life-threatening adverse effects greatly limit the safety of this route of administration.[41]

Inhaled short-acting agents have an onset of effect within minutes and peak effect in 30 to 90 minutes. Short acting β_2 agonist inhalers should be used as necessary to relieve symptoms. Salmeterol, the long acting agent has a much slower onset of effect (10 to 20 minutes) and a longer time to peak effect (2 to 4 hours). Formeterol has a more rapid onset (3 minutes) than salmeterol.[42] In contrast to the short acting agents, long acting β_2 –Adrenergic drugs are not to be used on demand but rather are prescribed on a twice- daily basis and are described as a long- term control medication.[43]

Slow release oral formulations of salbutamol and terbutaline are available and these increase the duration of activity of these bronchodilators considerably compared with conventional oral tablets.[44]

Adverse effects may occur after acute use or chronic regular use. Acute adverse effects are seen after oral and inhaled administration and are caused principally by β_2 receptor stimulation in skeletal muscle and in vascular smooth muscle, producing tremors, reflex tachycardia and headache and β_1 and β_2 stimulation in the heart, resulting in tachycardia and palpitations. General systemic side effects include

hypokalaemia and hyperglycaemia, increased free fatty acids, hypomagnesaemia, increased blood lactate and uterine relaxation. Tachyphylaxis to systemic effects usually occurs within 2 weeks with continued therapy.[45]

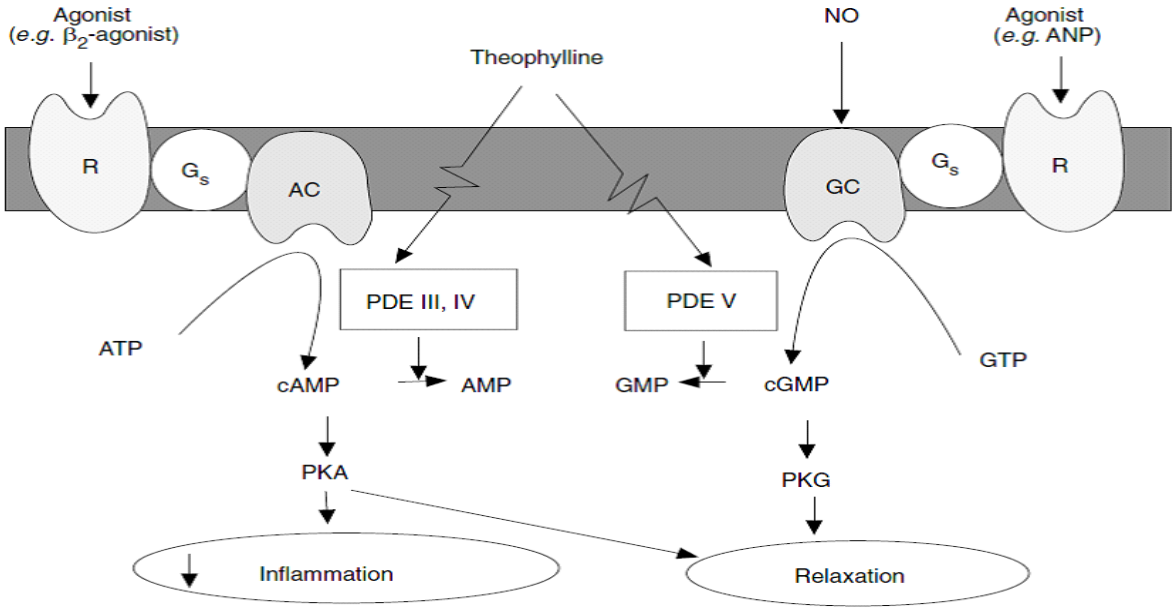


FIGURE 5: Mechanism of action of β_2 –adrenergic agonists & methylxanthines

METHYLXANTHINES

Methylxanthines have been used to treat acute and chronic asthma for more than 50 years; theophylline is the primary drug. Dyphylline, caffeine, and theobromine are methylxanthines with much weaker bronchodilator activity than theophylline, enprofylline, and doxofylline. Salts of theophylline have been developed to improve solubility and absorption. Only ethylenediamine salt of theophylline (aminophylline) is of clinical importance.

Theophylline exerts its bronchodilator effects via inhibition of phosphodiesterase (PDE). PDE III, IV, and V catalyse the breakdown of intracellular cAMP and cyclic 3', 5' cGMP, respectively. PDE III, IV, and possibly V are present in smooth

airway muscle, whereas PDE IV is the predominant isoenzyme in inflammatory cells. PDE III and IV inhibition increase cAMP, which opens k^+ channels; opening these channels contributes to smooth muscle relaxation.[46]Theophylline is now believed to have modest anti-inflammatory or immunomodulatory effects as well. Theophylline inhibits adenosine- stimulated release of mediators from mast cells at therapeutic serum concentrations. It also inhibits eosinophil activation and degranulation, decreases the total number of eosinophils, decreases vascular permeability and, enhances mucociliary clearance.[46, 47] Theophylline has been shown to increase the contractility of the diaphragm and render it less susceptible to fatigue, and also to increase maximal transdiaphragmatic pressure.[48]

Theophylline is administered orally, intravenously, and rectally although latter is rarely used because of unpredictable absorption.[47]A serum theophylline concentration of 10–20 μg/mL was recommended, since below this range bronchodilatation is unlikely and above it symptoms of toxicity are common.[49, 50]

Pharmacokinetics depends largely on factors influencing hepatic metabolism. Hyperthyroidism, cystic fibrosis, smoking, and ingestion of a high- protein, low carbohydrate diet are common conditions known to increase theophylline clearance, whereas age less than 1 year or over 60 years, congestive heart failure, prolonged fever, hypothyroidism, and liver disease are some conditions known to decrease theophylline clearance.[51] In most patients there is also a direct relationship between serum theophylline levels and side-effects, the most troublesome being nausea, vomiting, headache, nervousness and irritability. Because these toxic effects are common, the popularity of theophylline has declined markedly.[52, 53]

ANTI-CHOLINERGICS

The drugs of this category (muscarinic antagonists) most widely used in the treatment of reversible airways disease are ipratropium bromide and tiotropium bromide.[44]

Ipratropium bromide is a quaternary ammonium salt derived from atropine. Because inhaled atropine is highly absorbed across the respiratory epithelium, it causes many systemic anticholinergic effects, including tachycardia, nausea, dry mouth, constipation, and urinary retention. Unlike atropine, ipratropium is not significantly absorbed, and these adverse systemic effects are minimized. Nonetheless, inhaled ipratropium can cause dry mouth and gastrointestinal upset through its deposition in the mouth and inadvertent oral absorption.

Tiotropium, a long-acting anticholinergic agent, has been approved by the U. S. Food and Drug Administration (FDA) for the treatment of chronic obstructive pulmonary disease. Like ipratropium, tiotropium is a quaternary ammonium salt that produces few systemic effects because it is not systemically absorbed upon inhalation.

Atropine, ipratropium, and tiotropium are competitive antagonists at muscarinic acetylcholine receptors. Of the four muscarinic receptor subtypes expressed by the lung (M_1, M_2, M_3, and M_4), the excitatory M_3 receptor is the most important in mediating smooth muscle contraction and mucus gland secretion in the airway. Ipratropium and tiotropium antagonize the effect of endogenous acetylcholine at M_3 receptors, leading to bronchorelaxation and decreased mucus secretion. Tiotropium has a long duration of action largely because of its slow dissociation from M_1 and M_3 receptors.[21]

Ipratropium has a slower onset of action (1–2 hours for peak activity) than β_2-adrenoceptor agonists and thus may be more suitable for prophylactic use.

Compared with β_2-adrenoceptor agonists, ipratropium is generally at least as effective in chronic obstructive pulmonary disease but less effective in asthma.[54]

THE PREVENTERS

Drugs with anti-inflammatory properties used to influence the underlying inflammatory mechanisms of asthma.

SODIUM CROMOGLYCATE (CROMOLYN SODIUM) AND NEDOCROMIL SODIUM

Sodium cromoglycate and nedocromil sodium inhibit the IgE-mediated release of mediators from mast cells.The mechanism by which they inhibit mediator release at the cellular level is unclear but probably involves regulation of intracellular calcium by phosphorylation of a specific membrane protein that inhibits calcium influx into the cells. They also inhibit the release of mediators from eosinophils, alveolar macrophages, neutrophils, and monocytes. Adverse effects of cromolyn and nedocromil are rare and most often include transient bronchospasm, cough, and dry throat.[55]

The National Asthma Education and Prevention Program (NAEPP) guidelines recommend cromolyn or nedocromil only in mild persistent asthma, and they may be preferred initial anti-inflammatory therapy in children.[56]

LEUKOTRIENE MODIFIERS

The leukotriene modifiers (zileuton, zafirlukast, and montelukast) are the first new pharmacological class of drugs for treating asthma in more than 20 years.[57] Leukotriene modifiers block leukotriene- mediated effects, either by preventing the enzymatic conversion of arachidonic acid to LT A_4, as with zileuton, or by blocking the binding of leukotrienes to the $CysLT_1$ receptoe site, in the case of zafirlukast and montelukast. The leukotriene modifiers are administered orally and do not have

clinically significant effects when inhaled. Zileuton is dosed four times daily, zafirlukast twice daily, and montelukast once daily.[58] Leukotriene modifiers currently have no role in treating acute asthma but have been used as single-drug therapy to treat mild persistent asthma as an alternative after considering therapy with inhaled corticosteroids, cromolyn, or nedocromil.[59]

CORTICOSTEROIDS

With the new emphasis on anti-inflammatory therapy, corticosteroids, particularly inhaled, are now a cornerstone in asthma treatment. Corticosteroids have been used in the treatment of asthma for more than 40 years. They have many actions that may contribute to their effectiveness in controlling inflammation. [60]

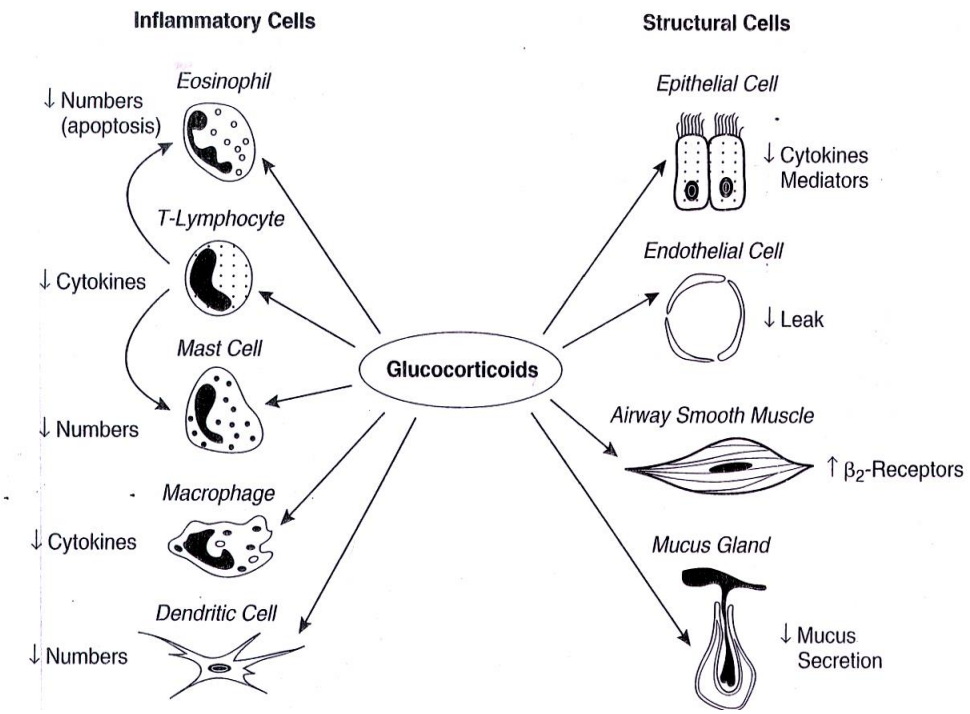


FIGURE 6: Effects of corticosteroids

Following the development of a number of glucocorticosteroids, prednisolone became the standard oral therapy, and hydrocortisone and methylprednisolone have become established as the most commonly chosen corticosteroids for intravenous administration. Prolonged use of systemically administered corticosteroids is limited by adverse effects like adrenal suppression and insufficiency, cushingoid habitus, fluid and electrolyte imbalances, growth suppression, hyperglycaemia, hypertension, osteoporosis, peptic ulcers. However, limited short courses may be necessary for treating acute exacerbations.

Beclomethasone dipropionate, budesonide, flunisolide, fluticasone propionate, and triamcinolone are inhaled glucocorticosteroids which have shown to reduce the inflammation and bronchial hyperresponsiveness of asthma, but with much lower potential for systemic toxicities than systemic administration. Local adverse effects with inhaled corticosteroid therapy include oropharyngeal candidiasis, coughing, dysphonia, and hoarseness. Auxiliary spacer devices used with MDIs reduce oropharyngeal deposition of the corticosteroid and reduce the incidence and severity of these effects. Mouth rinsing with water or antiseptics mouthwash after treatment can also reduce the risk of topical adverse effects.[55]In low doses of up to 400 μg daily; it is possible to detect evidence of systemic absorption and activity by assessment of hypothalamic–pituitary–adrenal axis function, [61] although these minor changes are of no clinical importance even after prolonged therapy.[62]

H_1-RECEPTOR ANTAGONISTS

Although effective in the treatment of allergic rhinitis, antihistamines have little place in the treatment of asthma. The evidence for and against the use of these drugs in asthma has been extensively reviewed and it is apparent that the few patients who may benefit from these compounds are young atopic individuals with mild seasonal

symptoms. Ketotifen is a commonly used drug, especially in underdeveloped countries. It has an inhibitory effect on mast cells similar to that of sodium cromoglycate. In challenge studies ketotifen has an immediate bronchoprotective effect, although there are no convincing clinical trial data to confirm its value in the long-term treatment of asthma. Like many of the early antihistamines, the most common side-effect of ketotifen is drowsiness, which occurs in over 20% of patients.[63]

BIOLOGIC THERAPIES FOR ASTHMA TREATMENT

Immediate hypersensitivity reactions such as those that provoke allergic asthma are dependent upon cross-linking of mast cell FcεR1-bound IgE by specific antigen. Clinically available biologic therapy for asthma is omalizumab, a humanized monoclonal antibody that blocks this step by binding free, circulating IgE in the region of its C3 domain, the site to which cell membrane FcεR1 binds. This prevents mast cell activation and degranulation, and also forms complexes with IgE.

It is generally thought that eosinophils are important and possibly essential to the development of asthmatic airway inflammation. IL- 5 is the key regulator of eosinophil trafficking to the inflamed airway. Mepolizumab and SCH55700 are two monoclonal antibodies to human IL-5. Altrakincept - a soluble recombinant IL-4 receptor, BAY-16- 9996 - a IL-4 and IL-13 receptor antagonist, Pascolizumab - an Anti-IL-4 antibody, anakinra -recombinant IL-1 and other recombinant IL-10, IL-12, IFN are undergoing clinical trials.[64]

METHYL XANTHINES

AMINOPHYLLINE

CHEMISTRY:

Aminophylline is a 2:1 complex of theophylline and ethylenediamine. Ethylenediamine improves solubility and is usually found as a dihydrate. Aminophylline has the chemical name 1H-Purine-2, 6-dione, 37-dihydro-1, 3-dimethyl compound with 1, 2-ethylenediamine (2:1) and is represented by the following structural formula.

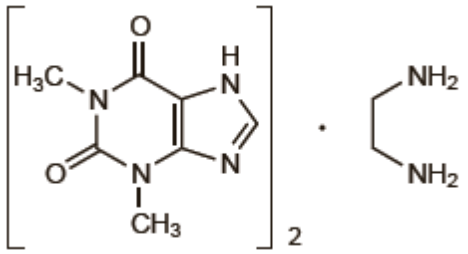


FIGURE 7: Structure of Aminophylline

PROPERTIES-It is more soluble in water than theophylline. It is white or slightly yellowish granules or powder, having a slight ammoniacal odor and a bitter taste. Its solutions are alkaline. The molecular formula of aminophylline dihydrate is C16H24N10O4.2 (H $_2$O).[65]

MECHANISM OF ACTION:

Like other methylated xanthine derivatives, aminophylline is both a competitive nonselective phosphodiesterase inhibitor which raises intracellular cAMP, activates

PKA, inhibits TNF-alpha and leukotriene synthesis, and reduces inflammation and innate immunity and non-selective adenosine receptor antagonist. [46, 47]

PHARMACOKINETICS:

Absorption- Rapidly and completely absorbed in solution or immediate-release.[65] The bioavailability of enteric coated oral tablets or capsules is incomplete and unpredictable while extended release oral tablets and capsules have bioavailability of 90- 100%.[66] C_{max} is 10 mcg/mL (5to15mcg/mL). T_{max} is 1 to 2 h. Food and antacid do not cause any clinically important changes; therapeutic range is 10 to 20 mcg/mL. Distribution- 40% protein bound (primarily albumin). Unbound theophylline distributes throughout the body water, but distributes poorly into body fat. Volume of distribution (V_d) is 0.45 L/kg (0.3 to 0.7 L/kg) based on ideal body weight. Freely passes across the placenta into breast milk and into cerebro spinal fluid.

Metabolism -Aminophylline does not undergo any measurable first-pass elimination. About 90% of dose is metabolized in the liver in adults and children older than 1 yr of age. Caffeine and 3-methylxanthine are the only theophylline metabolites with pharmacological activity.

Elimination - In neonates, approximately 50% of the theophylline dose is excreted unchanged in the urine. Beyond the first three months of life, approximately 10% of the theophylline dose is excreted unchanged in the urine. In adults, otherwise healthy non-smoking asthmatics, the half life is 6 hours.

INDICATIONS AND USAGE:

Orally given for reversible airflow obstruction associated with chronic asthma and other chronic lung diseases (Eg, chronic bronchitis, emphysema). Tab Aminophylline 300-700 mg in divided doses every 6-8 hrs.

Parenteral- Adjunct to inhaled beta-2 selective agonists and systemically administered corticosteroids for the treatment of acute exacerbations of the symptoms and reversible airflow obstruction associated with asthma and other chronic lung disease (eg, chronic bronchitis, emphysema). In adults, otherwise healthy nonsmokers, aminophylline is infused at a rate of 0.4 mg/kg/hr (not to exceed 900 mg/day unless plasma levels indicate the need for a larger dose).[65]

ADVERSE EFFECTS:

Rapid intravenous administration of therapeutic doses of aminophylline (500 mg) sometimes results in sudden death that is probably due to cardiac arrhythmias, and the drug should be injected slowly over 20 to 40 minutes to avoid severe toxic symptoms. These include headache, palpitation, dizziness, nausea, hypotension, and precardial pain. Additional symptoms of toxicity include tachycardia, severe restlessness, agitation, and emesis; these effects are associated with plasma concentrations of more than 20 µg/ ml. Focal and generalized seizures also can occur, sometimes without prior signs of toxicity. Most toxicity results from repeated administration of aminophylline by either oral or parenteral routes. Although convulsions and death have occurred at plasma concentration as low as 25 µg/ ml, seizures are relatively rare at concentration below 40 µg/ ml. The widespread use of sustained- release preparations of aminophylline has renewed emphasis on measures to prevent continued absorption, particularly the use of oral activated charcoal and sorbitol as a cathartic. However, when plasma concentration exceed 100 µg/ ml, invasive measures usually are required, especially hemoperfusion through charcoal cartridges.[2]

CONTRAINDICATIONS & PRECAUTIONS:

Aminophylline tablets are contraindicated in patients with a history of hypersensitivity to theophylline or other components in the product including ethylenediamine.

Pregnancy- Category C.

Lactation- Excreted in breast milk.

Children- Safe and effective -approved indications in children.

Elderly-Elderly patients are at increased risk of experiencing serious theophylline adverse reactions and toxicity compared with younger patients because of pharmacodynamic and pharmacokinetic changes associated with aging.

Theophylline should be used with extreme caution in patients with active peptic ulcer disease, seizure disorders, and cardiac arrhythmias. The dose of theophylline selected for initiation of therapy should be low and, if tolerated, increased slowly over a period of week or longer with the final dose guided by monitoring serum theophylline concentrations and the patient's clinical response.[65]

DRUG INTERACTIONS:

Drugs like propranolol, mexiletine, alcohol, allopurinol, erythromycin, clarithromycin, disulfiram, estrogen, ticlopidine, tacrine are known to increase the effect of aminophylline whereas drugs like carbamazepine, isoproterenol, sulfinpyrazone, Phenobarbital, rifampin decrease the effect.[51]

DOXOFYLLINE

CHEMISTRY:

Doxofylline is chemically designated as 7 (1, 3 dioxolone-2yl methyl) theophylline. Presence of a diaxolone group in position 7 differentiates it from theophylline.[67]

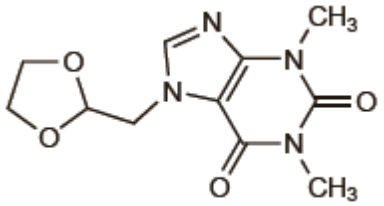


FIGURE 8: Structure of Doxofylline

MECHANISM OF ACTION:

Similar to theophylline, the mechanism of action doxofylline is related to the inhibition of phosphodiesterase enzymes. The increased levels of cyclic AMP consequent to this inhibition cause relaxation of smooth muscles.[46, 47] Doxofylline has greatly decreased affinities towards adenosine A_1 and A_2 receptors, unlike theophylline which explains its better safety profile (Fig 7). In experimental studies, doxofylline has shown potent anti-bronchospastic activity (2.5 to 10times) and less extra-respiratory effects than aminophylline.[68] Doxofylline does not interfere with calcium influx into the cells or antagonize calcium channel blockers.[69]

PHARMACOKINETICS:

Doxofylline achieves peak serum concentrations of 15.20 ± 1.73µg/ml after oral administration with a mean elimination half-life of 7.01 ± 0.80 hours. The half life of

>6 hours allows effective constant plasma levels with a twice daily dose of doxofylline.[70] Serum levels of 12-13µg/ml produce an optimal effect on airways.[69]

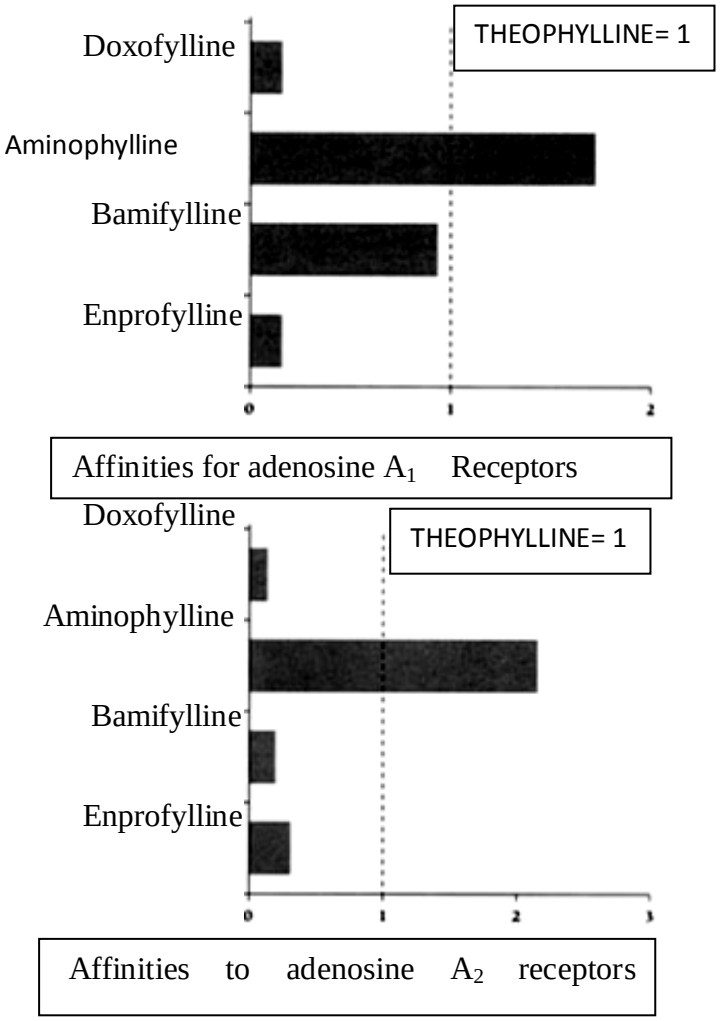


FIGURE 9: Affinities to adenosine receptors

ADVERSE EFFECTS:

Nausea, vomiting, epigastric pain, headache, irritability, tachycardia and insomnia may occur with doxofylline. Doxofylline is better tolerated than theophylline.

INDICATIONS AND USAGE:

Doxofylline is indicated in asthma and chronic obstructive pulmonary disease. The recommended dose is 400 mg b.i.d or t.i.d. in adults and 12 mg/kg daily b.i.d in children.[68]

CONTRAINDICATIONS:

- Hypersensitivity to doxofylline.
- Acute MI
- Hypotension.[70]

PULMONARY FUNCTION TESTS

The pulmonary function tests evolved as a volumetric experiment as early as 200 AD and underwent many modifications like pulmometer, spirometer, close-circuit spirometer till the introduction of the present day computerized spirometer.

Pulmonary function tests (PFT) provide objective and quantifiable measure of lung functions.[71] PFTs assessing range from simple standardized techniques that can be performed rapidly and accurately to detailed methods that are time consuming. Depending on the levels of increasing sophistication pulmonary function assessment can be conveniently divided into three levels.

- **FIRST LEVEL INCLUDES**
    a) Measurement of ventilator functions (Spirometry)
    b) Assessment of gas exchanging ability of the lungs by measurement of arterial blood gas tensions
- **SECOND LEVEL INCLUDES**
    a) Measurement of Static Lung Volumes – FRC, RV, TLC.
    b) Estimation of diffusing capacity of the lungs
- **THIRD LEVEL INCLUDES**
    a) Airway resistance and pulmonary compliance.
    b) Pressure-Volume relationship of the lungs.
    c) Ventilation-perfusion relationship.
    d) Ventilation response to oxygen and carbon dioxide.[72]

For describing the events of pulmonary ventilation, the air in the lungs has been subdivided into four volumes and four capacities.

- Lung Volume TV - Tidal Volume
  IRV - Inspiratory Reserve Volume
  ERV - Expiratory Reserve Volume
  RV - Residual Volume
- Pulmonary Capacities IC - Inspiratory Capacity
  FRC - Functional Residual Capacity
  TLC - Total Lung Capacity
  VC - Vital Capacity

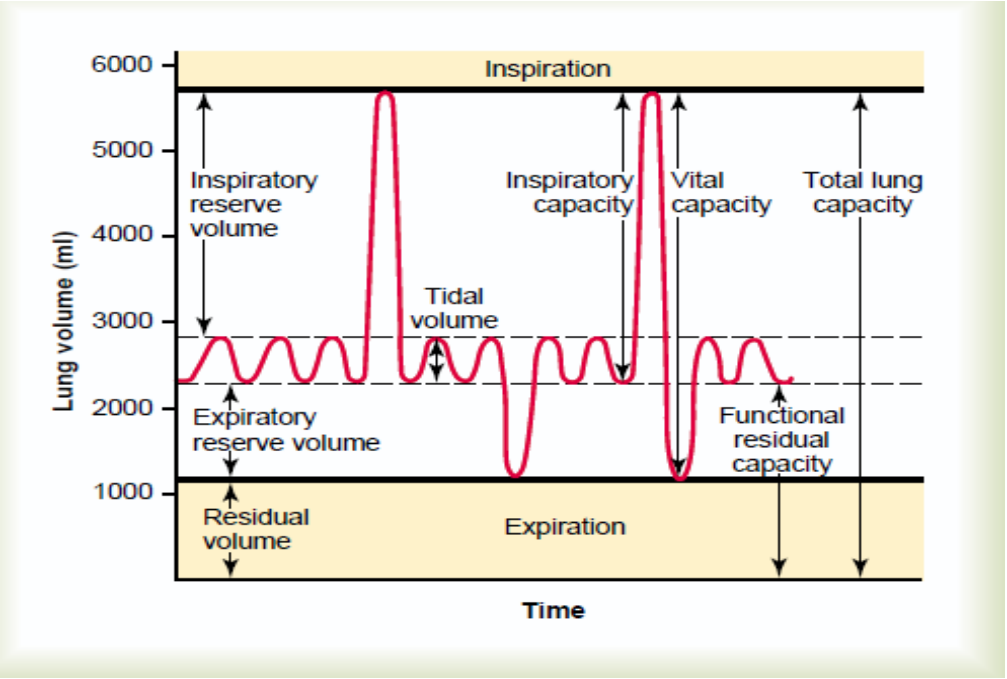


FIGURE 10: Lung volumes and capacities

TABLE 2:Lung volumes

LUNG VOLUMES	NORMAL VALUES (Adults) in ml	
	MALES	FEMALES
1.Tidal Volume: The volume of air inspired or expired with each normal breath.	500	500
2. Inspiratory Reserve Volume: The air inspired with a maximal effort in excess of the tidal volume.	3300	1900
3.Expiratory Reserve Volume: The volume expelled by an active expiratory effort after passive expiration is the expiratory reserve volume.	1000	700
4. Residual Volume : The volume of air in the lungs after a maximal expiratory effort.	1200	1100

TABLE 3: Lung capacities

PULMONARY CAPACITIES	NORMAL VALUES (Adults) in ml	
	MALES	FEMALES
1. Inspiratory Capacity: Maximum volume of air that can be inspired after a normal expiration. TV + IRV	3500	2200
2. Functional Residual Capacity: The amount of air that remains in the lung at the end Of normal expiration ERV + RV	2300	1800

3. Total Lung Capacity: The maximum volume to which the lungs can be expanded with the greatest possible effort. VC + RV	5800	4200
4. Vital Capacity: The largest amount of air that can be expired maximally after a maximal inspiratory effort.[73,74]	4800	3100

Of the above, the vital capacity, tidal volume, inspiratory reserve volume, expiratory reserve volume, and inspiratory capacity are measured directly by simple spirometry where as residual volume, functional residual capacity and total lung capacity can be measured by indirect methods like inert gas (usually helium) dilution techniques, nitrogen washout technique and Body Plethysmography.[75]

The cornerstone of all pulmonary function tests is clinical spirometry. Spirometry is measured by different spirometers. The commonest being the

1. Simple spirometer/student spirometer/vitalograph.
2. Recording spirometer.
3. Wright's peak flow meter
4. Computerised spirometer.[76]

SPIROMETRY (DYNAMIC LUNG VOLUME MEARUSEMENT):

Spirometry in Greek means, 'to measure breathing'. It is the measurement of the movement of air into and out of the lungs during various breathing maneuvers.[1]

Ventilatory function tests assessed by the rate at which the lung volume changes, during a forced breathing maneuver are

1. Forced Vital Capacity Maneuver.
2. Maximal Voluntary Ventilation Maneuver.[77]

Forced Vital Capacity maneuver measures airflow out of fully inflated lungs. In this maneuver, the subjects inhales maximally to total lung capacity and then exhales as rapidly and completely as possible to residual volume. In full inspiration, the lungs are filled by muscular force, to expand the lungs, thorax and stretches the chest to its maximum and the lungs expand passively. After this a full forced expiration rapidly empties the lungs into a device that records flow over time. Normal lungs empty in at least 6 seconds. Expiratory airflow is a function of muscular effort, elastic recoil of lungs and thorax, small airways and large airways function, and interdependence between small airway and the surrounding alveolar attachments.[78]

FVC maneuver can be displayed in two different ways

1. Spirogram
2. Flow – volume loop

SPIROGRAM: In spirogram method, the volume of air exhaled is plotted against time as shown in Fig 9.

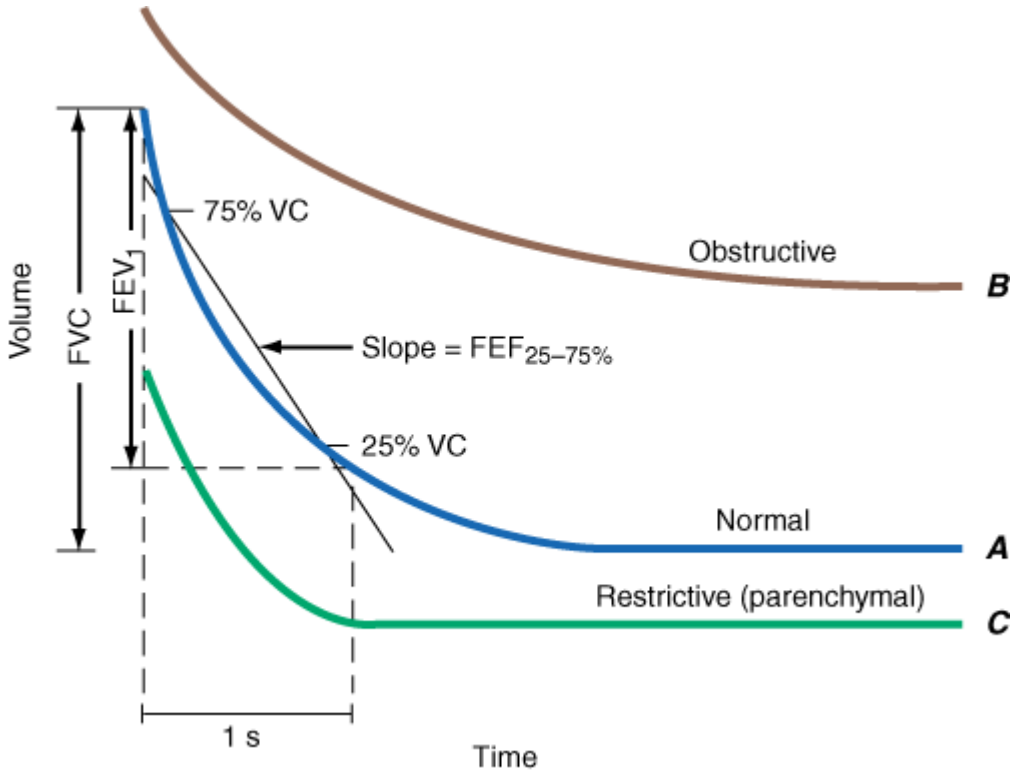


FIGURE 11: Spirogram

This spirogram provides four major test results.

1. Forced Vital Capacity – It is the total volume of air that is exhaled during a forced exhalation after maximal inhalation and it is reported in liters.

2. Forced Expiratory Volume in 1st second - (FEV_1). This is the fraction of vital capacity during the first second of a forced expiration. Normally 80 -85% of the forced vital capacity is expired in the first second (3-4.5 L), 95-97% in second seconds (FEV_2) and 97-100% in third seconds (FEV_3). This test detects generalized

airway obstruction.[79] FEV_1 is the best characterized test of respiratory function; information on changes with age, gender, ethnic group, growth, and disease is more developed than for any other test, repeatability is good, and it provides useful information across the whole range from normal to advanced disease. The FEV_1 is used mainly to assess intrathoracic airways obstruction in clinical practice or in epidemiological surveys. A major application of FEV_1 is the assessment of bronchodilators and bronchoconstrictor responses. Reduction of FEV_1 also may reflect reduction in TLC (restrictive disease of the lungs). This distinction is assessed by measuring FEV1/FVC. FVC is less repeatable than FEV_1 in airflow obstruction. Therefore for follow up of mild airways obstruction the change in FEV_1 usually provides more reliable information.[80]

3.Forced Expiratory Flow 25-75%(average mid-maximal expiratory flow) – This is the average flow rate over the middle section of the vital capacity is called MMEF (mid- maximal expiratory flow) or FEF 25-75% (forced expiratory flow from 25-75% of the vital capacity). This is calculated from the spirogram by dividing the vital capacity into quarters, drawing a line from the first (25%) and third (75%) quartiles. This indicates the patency of small airways.

4. Ratio of FEV_1 to FVC- FEV_1 expressed as a percentage of the FVC

FEV_1/FVC >70% - Normal

<70% - Mild obstruction

<60% - Moderate obstruction

<50% - Severe obstruction

FLOW-VOLUME LOOP:

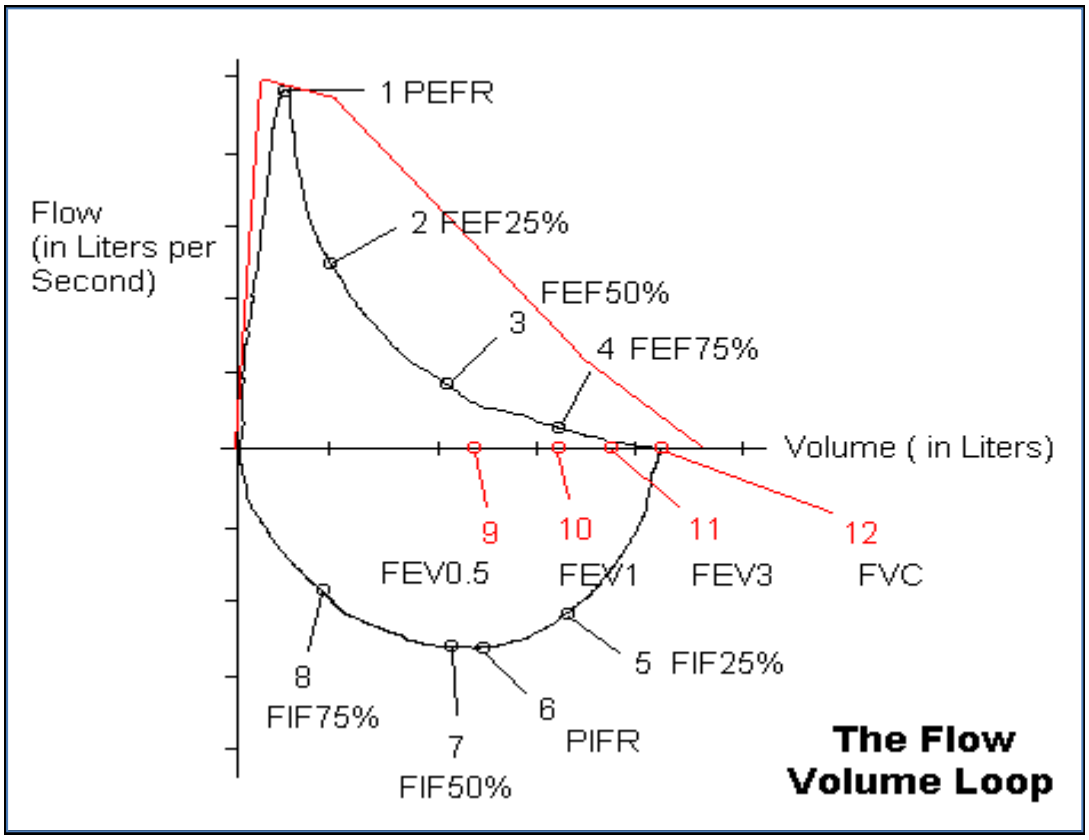


FIGURE 12: Flow-volume loop

FVC maneuver can be displayed by recording the instantaneous flow rate versus volume. This is called the flow volume meter loop, which is shown in Fig 9. Flow-volume loop can record instantaneous flow both during exhalation and during inspiration. The Flow-volume loop is recorded by asking the subject to take a maximal inspiration to total lung capacity and then to breath out as fast and rapidly as can until he can exhale no further (a maximal exhalation to residual volume) then take a rapid and maximal inspiration. Flow rates above the horizontal line are expiratory flow volume loop; flow rates below the horizontal line are inspiratory

flow-volume loop. Total lung capacity is the point at which inspiration is maximal. Residual volume is the point at which exhalation is maximal.

The flow-volume loop yields four main pulmonary function tests data:

- Forced Vital Capacity - It is the total volume of air that is exhaled during a forced exhalation after maximal inhalation is called the FVC and reported in liters.
- Peak Expiratory Flow Rate- It is the maximum flow rate achieved during the maneuver. It is measured in liters/min or L/sec. Normal values – 500 L/min

Peak flow is largely a function of the caliber of the airways. It greatly depends on expiratory muscle strength and the patient effort and coordination.

- Forced Expiratory Flow 50%- Volume achieved after exhaling 50% of the total FVC
- Forced Mid Expiratory Flow ($FEF_{25-75\%}$) - Flow measured over the middle half of the FVC.

A normal value averages 4.5 to 5.0 L/sec.

It is often referred to as effort independent. This flow rates may also decrease with truly maximum effort, when compared with slightly sub maximal effort. This phenomenon is called negative effort dependence. This measurement is a sensitive indicator of early obstruction in the small distal airways.[79]

MATERIALS AND METHODS:

A study was conducted from 1st December 2008 to 31st May 2010 on outpatients with asthma presenting to the department of Medicine.

Source of data (sample):

Patients attending to the department of Medicine at R.L.Jalappa Hospital and Research Center attached to Sri Devaraj Urs Academy of Higher Education and Research Tamaka, Kolar with clinical diagnosis of chronic bronchial asthma (mild to moderate asthma).

Data collection:

A proforma containing detailed information on each patient was prepared according to the protocol designed for the study. Informed consent was taken from all the patients included in the study. Ethical clearance was obtained from the institutional ethics committee.

Inclusion Criteria:

1. Patients of either sex.
2. Patients in the age group of 20-40 years.
3. Patients with reversible obstructive airway disease having FEV 1 of 60% and above.

Exclusion Criteria:

1. Pregnant and nursing women.
2. Patients with serious concomitant respiratory infection, cardiovascular, renal, hepatic or metabolic diseases.

3. Patients who had taken drugs known to affect Theophylline clearance.
4. Patients on Glucocorticoids and long acting beta 2 agonists.

A total of 60 patients with mild to moderate asthma were enrolled in the study. They were randomized into 2 groups of 30 each to receive either Tab. Aminophylline 225mg (Modi-Mundi Pharm) or Tab. Doxofylline 400mg (Micro Labs Limited) following baseline pulmonary function test (PFT).

Relevant data were taken from the patients. The data included hospital number, name, age of the patient, history of presenting illness. The Proforma also enlisted general physical examination, vital signs and systemic examination. Height was measured in standing position in centimeters and weight was measured in kilograms. PFT was done at baseline and 4hrs after drug administration and Spirometric response was assessed. Changes in Heart rate, Blood Pressure and respiratory rate were also assessed. Adverse effects of both the drugs were recorded.

Pulmonary Function tests were performed using Medspiror, which is a Personal Computer based spirometer with flow transducer (Recorders and Medicare Systems) in all the subjects.

Transducer Assembly: It is a flow transducer, which is bi-directional for both exhale and inhale maneuver. Mouthpiece is pushed on the transducer assembly and while removing, it has to be pulled out without rotating it. Hand/fingers were avoided on backside mesh while doing maneuver. It is plug and go computer based spirometry.

Test was performed in standing position. Reference values for spirometry were based on age, sex, height and weight provided in the software.

The whole procedure was explained and demonstrated to the subject before the testing. Later the subject was asked to perform the Forced Vital Capacity maneuver. FVC was recorded after a maximal inspiration when the subject expires forcefully with maximum expiration into the mouthpiece. A minimum of 3 acceptable FVC maneuvers was performed and the best maneuvers was selected and accepted. Acceptability criteria was

- Full inhalation before start of test
- Satisfactory start of exhalation: Maximal effort exerted and no hesitation
- No cough during the first second of maneuver
- No early termination of exhalation
- A minimum exhalation time of 6 seconds is recommended or a one second with no change in volume.

After scrutinizing the flow-volume curve and time-volume curve, the parameters derived were FVC, FEV_1, FEV_1/ FVC, PEFR and $FEF_{25-75\%}$. Objectively based on FEV_1 asthma was categorized as

- Mild - $FEV_1 \geq 80\%$ predicted
- Moderate - FEV_1 60- 80% predicted
- Severe - $FEV_1 \leq 60\%$ predicted

Investigations like Chest X-ray and ECG were done as and when required.

Data were analyzed descriptively. Efficacy of the treatments based on PFT assessment and changes in Heart rate, Blood Pressure & respiratory rate within and between the groups was analyzed by paired and unpaired-T test respectively. A P-value of < 0.05 was considered significant.

RESULTS

TABLE 4 :AGE DISTRIBUTION

	Aminophylline Group n=30	**Doxofylline Group** n=30
Age (years)	32.07±6.913	33.40±6.162

Table 4 shows the age distribution in two treatment groups. The patients were balanced with respect to age. The mean age ± SD was 32.07± 6.913 and 33.40 ± 6.162 in the aminophylline and doxofylline group respectively and there was no relevant statistical difference between the groups.

TABLE 5: GENDER WISE DISTRIBUTION

Gender	**Aminophylline Group** n=30	**Doxofylline Group** n=30
Male (%)	15(50)	16(53.3)
Females (%)	15(50)	14(46.7)

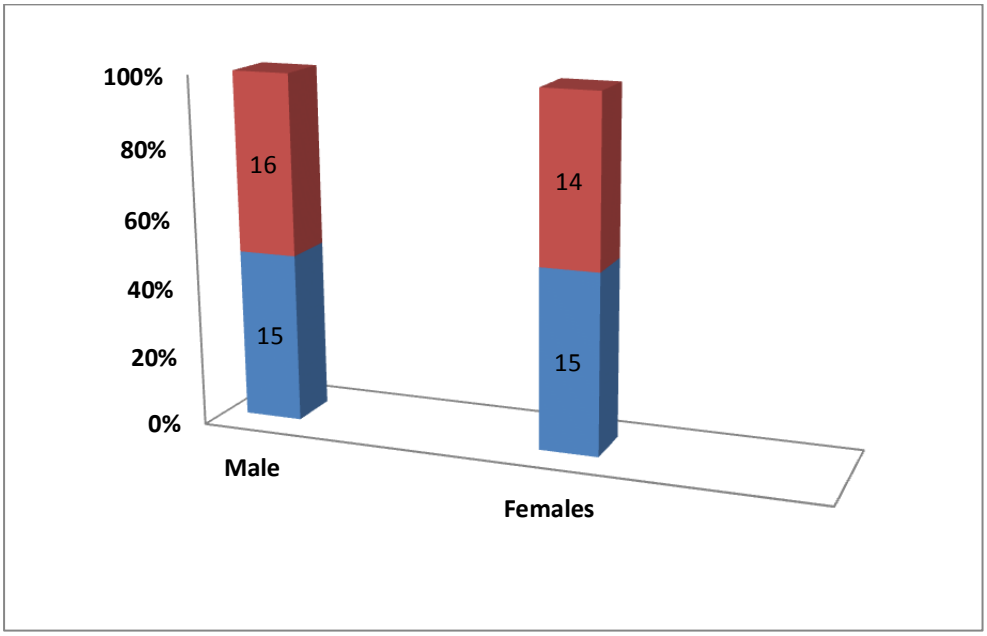


FIGURE 13 - GENDER DISTRIBUTION

Table 5 & Figure 13 shows gender distribution between the groups. The gender wise distribution was comparable between the groups.

TABLE 6 : ASTHMA SEVERITY

Asthma Severity- PFT (FEV_1)	AMINOPHYLLINE		DOXOFYLLINE	
	No.	%	No.	%
Mild	5	16.7	2	6.7
Moderate	25	83.3	28	93.3
Total	30	100	30	100

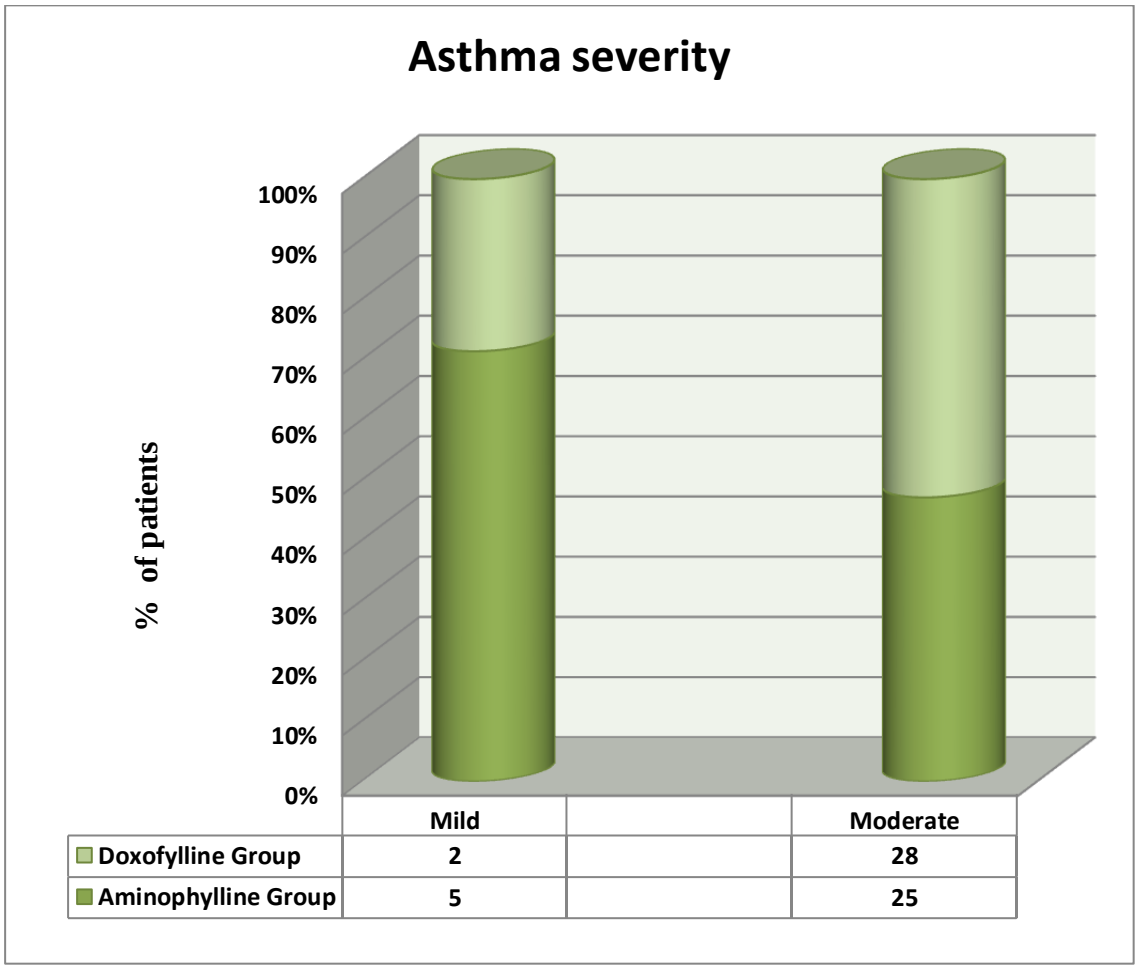


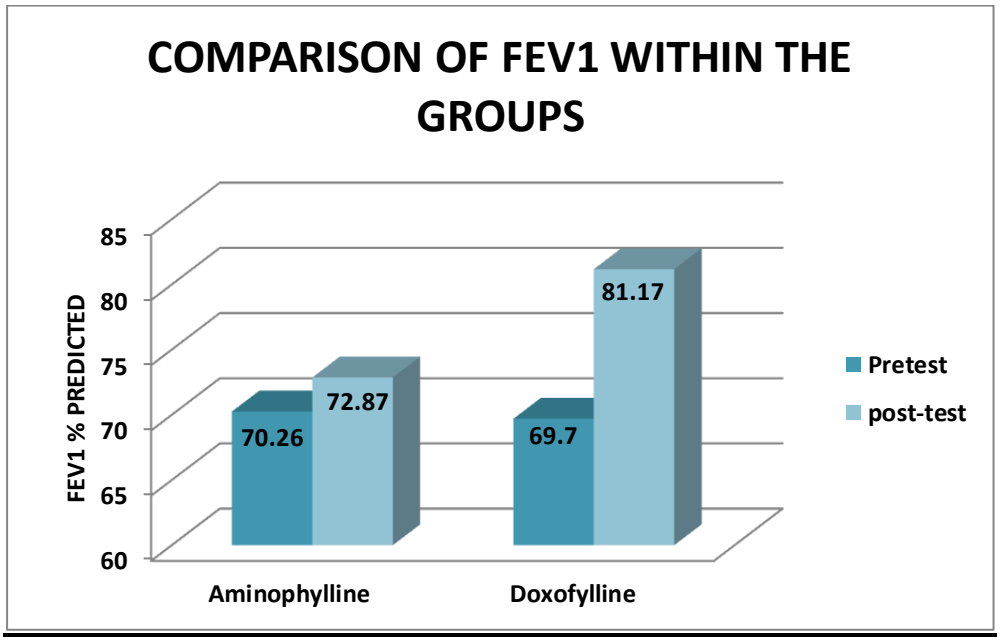
FIGURE-14

Table 6 and figure 14 shows the severity of asthma in both the treatment groups. Majority of the patients in both the groups had asthma of moderate severity i.e. 25 (83.3%) and 28 (93.3%) in aminophylline and doxofylline group respectively.

TABLE 7 : FEV_1 % PREDICTED VALUES – COMPARISON WITHIN THE GROUPS.

FEV_1	AMINOPHYLLINE			DOXOFYLLINE		
	Mean ± SD	% change from baseline	p-value	Mean ± SD	% change from baseline	p-value
BASELINE	70.26 ±8.372	----	----	69.70±6.949	----	----
POST TEST	72.87±9.677	3.71 %	0.002*	81.17±9.018	16.4 %	<0.001*

* P-value <0.05 is significant.



* P-value <0.05 is significant.

FIGURE-15

Table 7 and Figure 15 shows the comparison of FEV_1 within the groups. There was significant improvement in FEV_1 (%-Predicted) in both the treatment group compared to baseline. The p value was 0.002 and < 0.001 in aminophylline and doxofylline group respectively.

TABLE 8: FEV_1 % PREDICTED VALUES – COMPARISON BETWEEN THE GROUPS.

FEV_1	AMINOPHYLLINE Mean±SD	DOXOFYLLINE Mean±SD	P-VALUE
BASELINE	70.26 ±8.372	69.70±6.949	0.802
POST TEST	72.87±9.677	81.17±9.018	0.001*

* P-value <0.05 is significant.

Table 8 shows the comparison of FEV_1 % predicted values between the groups. Baseline FEV_1 values were comparable between the groups. There was significant improvement in FEV_1 in doxofylline group (p-0.001) compared to aminophylline group.

TABLE 9 : FVC - % PREDICTED VALUES – COMPARISON WITHIN THE GROUPS.

FVC	AMINOPHYLLINE			DOXOFYLLINE		
	Mean ± SD	% change from baseline	p-value	Mean ± SD	% change from baseline	p-value
BASELINE	64.83 ± 9.542	----	----	62.47 ± 9.709	----	----
POST TEST	65.23 ± 9.825	0.6%	0.710	72.43 ±10.776	15.9%	<0.001*

* P-value <0.05 is significant.

Table 9 shows the comparison of FVC within the groups. There was significant improvement in FVC (%-Predicted) in Doxofylline group compared to baseline but not in Aminophylline group. The p value was 0.701 and < 0.001 in aminophylline and doxofylline group respectively.

TABLE 10: FVC - % PREDICTED VALUES --COMPARISON BETWEEN THE GROUPS.

FVC	AMINOPHYLLINE Mean±SD	DOXOFYLLINE Mean±SD	P-VALUE
BASELINE	64.83 ± 9.542	62.47 ± 9.709	0.605
POST TEST	65.23 ± 9.825	72.43 ± 10.776	0.009*

* P-value <0.05 is significant.

Table 10 shows the comparison of FVC % predicted values between the groups. Baseline FVC values were comparable between the groups. There was significant improvement in FVC in doxofylline group (p-0.009) compared to aminophylline group.

TABLE 11: PEFR - % PREDICTED VALUES – COMPARISON WITHIN THE GROUPS.

PEFR	AMINOPHYLLINE			DOXOFYLLINE		
	Mean ± SD	% change from baseline	p-value	Mean ± SD	% change from baseline	p-value
BASELINE	48.80 ± 11.109	----	----	52.20 ± 12.050	----	----
POST TEST	55.00 ±12.204	12.7%	0.008*	61.8 ± 14.944	18.3%	<0.001*

* P-value <0.05 is significant.

Table 11 shows the comparison of PEFR within the groups. There was significant improvement in PEFR (%-Predicted) in both the treatment group compared to baseline. The p value was 0.008 and < 0.001 in aminophylline and doxofylline group respectively.

TABLE 12 : PEFR- % PREDICTED VALUES --COMPARISON BETWEEN THE GROUPS.

PEFR	AMINOPHYLLINE Mean±SD	DOXOFYLLINE Mean±SD	P-VALUE
BASELINE	48.80 ± 11.109	52.20 ± 12.050	0.261
POST TEST	55.00 ± 12.204	61.8 ± 14.944	0.059

* P-value <0.05 is significant.

Table 12 shows the comparison of PEFR % predicted values between the groups. Baseline PEFR values were comparable between the groups. There was no significant improvement in PEFR between the two groups.

TABLE 13 : $FEF_{25-75\%}$-% PREDICTED VALUES – COMPARISON WITHIN THE GROUPS.

$FEF_{25-75\%}$	AMINOPHYLLINE			DOXOFYLLINE		
	Mean ± SD	% change from baseline	p-value	Mean ± SD	% change from baseline	p-value
BASELINE	60.73 ± 16.036	----	----	65.80 ± 16.653	----	----
POST TEST	64.97 ± 14.801	6.98%	0.152	74.1 3 ±16.887	12.6%	0.002*

* P-value <0.05 is significant.

Table 13 shows the comparison of $FEF_{25-75\%}$ within the groups. There was significant improvement in $FEF_{25-75\%}$ (%-Predicted) in Doxofylline treated group compared to baseline but not in Aminophylline group. The p value was 0.152 and 0.002 in aminophylline and doxofylline group respectively.

TABLE 14 : $FEF_{25-75\%}$ - % PREDICTED VALUES --COMPARISON BETWEEN THE GROUPS.

$FEF_{25-75\%}$	AMINOPHYLLINE Mean±SD	DOXOFYLLINE Mean±SD	P-VALUE
BASELINE	60.73 ± 16.036	65.80 ± 16.653	0.235
POST TEST	64.97 ± 14.801	74.1 3 ± 16.887	0.029*

* P-value <0.05 is significant.

Table 14 shows the comparison of $FEF_{25-75\%}$ % predicted values between the groups. Baseline $FEF_{25-75\%}$ values were comparable between the groups. There was significant improvement in $FEF_{25-75\%}$ in doxofylline group (p-0.029) compared to aminophylline group.

TABLE 15: FEV_1/FVC - %PREDICTED VALUES – COMPARISON WITHIN THE GROUPS.

FEV_1/FVC	AMINOPHYLLINE			DOXOFYLLINE		
	Mean ± SD	% change from baseline	p-value	Mean ± SD	% change from baseline	p-value
BASELINE	109.13 ± 9.989	----	----	112.93 ±10.609	----	----
POST TEST	112.33 ± 7.631	2.7%	0.101	112.57 ± 8.756	-0.3%	0.733

* P-value <0.05 is significant.

Table 15 shows the comparison of FEV_1/FVC within the groups. There was no significant improvement in FEV_1/FVC (%-Predicted) in both treatment group compared to baseline. The p value was 0.101 and 0.733 in aminophylline and doxofylline group respectively.

TABLE 16 : FEV_1/FVC - % PREDICTED VALUES --COMPARISON BETWEEN THE GROUPS.

FEV_1/FVC	AMINOPHYLLINE Mean±SD	DOXOFYLLINE Mean±SD	P-VALUE
BASELINE	109.13 ± 9.989	112.93 ± 10.609	0.159
POST TEST	112.33 ± 7.631	112.57 ± 8.756	0.913

* P-value <0.05 is significant.

Table 16 shows the comparison of FEV_1/FVC % predicted values between the groups. Baseline FEV_1/FVC values were comparable between the groups. There was no significant improvement in FEV_1/FVC in between the groups.

TABLE 17 : VITAL PARAMETERS

Vitals	Aminophylline Group		Doxofylline Group	
	Pre treatment Mean±SD	Post treatment Mean±SD	Pre treatment Mean±SD	Post treatment Mean±SD
H.R	77.13±4.599	78.30±5.059	77.33±5.542	78.57±4.974
S.BP	119.07±5.889	120.20±5.997	116.27±6.638	116.80±6.531
D.BP	79.07±4.571	79.67±4.490	78.13±4.981	79.33±4.956
R.R	18.63±1.426	19.63±1.426	18.57±1.501	18.73±1.507

The vital parameters were comparable at baseline and there was no significant change in Heart rate , Blood Pressure and Respiratory Rate following treatment in both the groups.

TABLE 18 : COMPARISON OF ADVERSE EFFECTS

Adverse effects	Aminophylline	Doxofylline
Headache	15	9
Nausea	6	5
Heart Burn	4	1
TOTAL NO OF PATIENTS	19	13

Table 18 shows the adverse effects in both treatment groups. The most common adverse effect reported was headache 15(50%) in Aminophylline group and 9(30%) in Doxofylline group. All the adverse events were mild in nature and involved 19 (63%) and 13(43%) patients receiving Aminophylline and Doxofylline respectively.

DISCUSSION

Asthma is a chronic disease; management involves prophylactic measures to reduce inflammation and airway resistance and to maintain airflow, as well as specific regimens for the treatment of acute attacks. Measurements of lung function play an important part in determining treatment and patients are encouraged to monitor their own disease by using a simple peak flow meter to measure PEF and adjust their therapy accordingly. Spirometry is used to measure airflow limitation and reversibility in hospitals.

Drug therapy is preferably given by inhalation to deliver the drugs directly to the desired site of action. The standard drugs used in the management of asthma are the $beta_2$ agonists and corticosteroids.[39]

Methylxanthines have been used to treat acute and chronic asthma for more than 50 years; theophylline is the primary drug. Especially helpful in resource restricted settings, being one of the few drugs that can be administered orally.[67] Dyphylline, caffeine, and theobromine are methylxanthines with much weaker bronchodilator activity than theophylline, enprofylline, and doxofylline. Ethylenediamine salt of theophylline (aminophylline) has been developed to improve solubility and absorption.[46] Sustained Release formulation provides consistent serum levels and better therapeutic control in comparison to conventional tablets.[81] The present study was undertaken to compare the efficacy and safety profile of sustained release oral Aminophylline v/s conventional oral Doxofylline. The data was analyzed and the results are discussed below.

Asthma can occur at any age. However, in half the cases, the onset is before 10 years of age.[11]

In our study, the mean age of the patients in the Aminophylline group was 32.07±6.913years, while that in the Doxofylline group was 33.40±6.162. In both the study groups the enrolled patients were aged between 20 to40. The data collected was age matched. The prevalence among males was slightly higher than among females according to the National Family Health Survey-2 report.[12] In our study, 31 patients were male and 29 were female and gender wise distribution was comparable between the treatment groups.

In the present study, majority of the patients in both the groups had asthma of moderate severity i.e. 25 (83.3%) and 28 (93.3%) in aminophylline and doxofylline group respectively.

The FEV_1 and FVC baseline values in both the treatment groups were less. The obstruction in asthma reduces the vital capacity. The obstruction is due to the chronic inflammation, which in turn causes smooth muscle hypertrophy and bronchial hyperactivity leading to airflow limitation. There was significant increase in FEV_1 ($p < 0.001$) and FVC ($p < 0.001$) in Doxofylline group after treatment versus baseline. These findings were similar to the observation of Dolcetti A *et al.*1988[82], Bagnato *et al.*1989[68], Goldstein MF *et al* 2002[4]. In Aminophylline group there was significant increase in FEV_1 ($p < 0.002$) but not in FVC. This finding was similar to the observation of Greening AP *et al* 1981[83], Chen CY *et al* 2005[3]. Changes in FEV_1 and FVC 4 hours after the administration of treatments versus baseline exhibited statistically significant improvement in doxofylline group compared to aminophylline group (p 0.001, 0.009). Studies comparing oral doxofylline and aminophylline are lacking.

The PEFR also showed low baseline values in both the treatment groups. The decreased PEFR function is due to the bronchial inflammation. PEFR value indicates the function of large airways. There was significant improvement in PEFR in both the treatment groups compared to baseline (Aminophylline group p-0.008 and Doxofylline group p-<0.001). Studies of Chen CY *et al* 2005[3], , Melillo G *et al* 1989[84] with aminophylline treatment, Goldstein MF *et al* 2002[4] with doxofylline treatment showed the similar PEFR values. There was increase in PEFR value more in Doxofylline compared to Aminophylline group but not significant.

The $FEF_{25-75\%}$ value significantly improved from baseline in Doxofylline group and also compared to Aminophylline group. $FEF_{25-75\%}$ is an index of small airway function of < 2mm diameter. Newly developed techniques of physiologic measurement have focused on assessing the role of lung periphery, and this distal site has now been recognized as a predominant site of airflow obstruction in asthmatics. It is now widely accepted that in asthmatics, recruitment of inflammatory cells, in particular eosinophils and T cells, also occur in the distal lung and the lung parenchyma.[85]

The mean and standard deviation value of FEV_1/FVC % in Aminophylline and Doxofylline was 109.13 ± 9.989 and 112.93 ±10.609 respectively. There was no significant difference in this ratio. In both groups FVC was increased and FEV_1 was also proportionately increased. Hence the FEV_1/FVC ratio was within normal limits. This explains the absence of significance within the two groups and therefore FEV_1/FVC ratio parameter will not be an important marker for pulmonary dysfunction. This parameter was not considered in Goldstein MF *et al* 2002.[4] In Panuccio P *et al* 1989[86]study, this ratio was significantly more in Doxofylline group

because the FEV_1 value was significanty increased than in comparison to the FVC increase.

There was no significant difference in heart rate, respiratory rate and blood pressure.

When we assessed the adverse effects, we observed that they occurred more frequently with aminophylline (63 %) than with doxofylline (43 %) but were mild. Headache, nausea and heart burn were noted. Headache was the most commonly reported adverse event in the overall study population. Bagnato *et al.*1989[68], Dini FL *et al* 2001[87], Goldstein MF *et al* 2002[4] studies have shown the same results. Doxofylline appears to have decreased affinities towards A_1 and A_2 receptors, which may account for its better safety profile.

CONCLUSION

The results of the present study show that administration of oral Doxofylline 400mg single dose is more effective and safe than sustained release Aminophylline 225 mg tablet. Doxofylline treatment has exhibited two characteristics that may expand its usefulness in the clinical setting. First, it produces improvements in airflow obstruction better than aminophylline with single dose and can be useful in acute attacks. Second, it has a favorable tolerability profile that suggests that this drug might be of particular benefit in selected groups of asthmatics, especially those with gastrointestinal intolerance. Since doxofylline was associated with remarkable bronchodilation, symptom relief and potentially less adverse events, it seems to be a good alternative to aminophylline therapy in the management of patients with chronic bronchial asthma.

SUMMARY

The aim of the study was to evaluate the efficacy and safety between aminophylline and doxofylline in the management of chronic bronchial asthma.

A study was conducted on 60 patients of whom 30 patients were assigned to Aminophylline 225 and the other 30 patients received doxofylline 400 mg.

Patients were in the 20–40 years age group, with the mean age being 32.07±6.913years in the Aminophylline group while that in the Doxofylline group was 33.40±6.162. Males and females were equally distributed in both the groups. Majority of the patients in the study had moderate asthma severity. When pulmonary function test parameters between the groups were compared, a significant improvement was observed in the Doxofylline group in FEV_1 (0.001), FVC (0.009), $FEF_{25-75\%}$ (p 0.029) percentage predicted value. Both the treatments showed significant improvement in FEV_1, PEFR. Doxofylline treated patients also showed improvement in FVC and $FEF_{25-75\%}$.

Adverse events were present in both groups but were mild in nature. Headache, nausea and heart burn were reported more in aminophylline treated group compared to doxofylline group.

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PROFORMA

DATE :

NAME : OUT PATIENT NO :

AGE :

SEX :

ADDRESS :

OCCUPATION :

COMPLAINTS :

PAST HISTORY : H/O ALLERGY

DRUG HISTORY :

FAMILY HISTORY:

PERSONAL HISTORY:

GENERAL PHYSICAL EXAMINATION:

HEIGHT ;

WEIGHT :

VITALS	PRE MEDICATION	POST MEDICATION
Heart rate,		
Blood pressure		
Respiratory rate		

SYSTEMIC EXAMINATION;

RS:

CVS:

CNS:

Per abdomen:

INVESTGATIONS: Chest X-ray, ECG (if required)

PULMONARY FUNCTION TEST:

Variables	Aminophylline 225 mg		Doxofylline 400 mg	
	PRE MEDICATION	POST MEDICATION	PRE MEDICATION	POST MEDICATION
FEV1				
FVC				
PEFR				
FEF25% -75%				
FEV_1/FVC				

ADVERSE EFFECTS

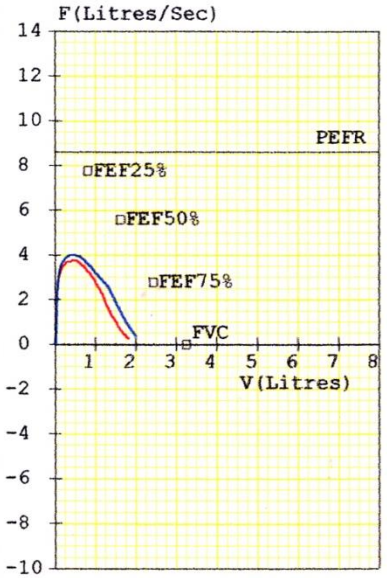
Headache	
Nausea	
Vomiting	
Gastrointestinal Discomfort	
Tremors	
Palpitations	
Persistence of Symptoms	
Others	

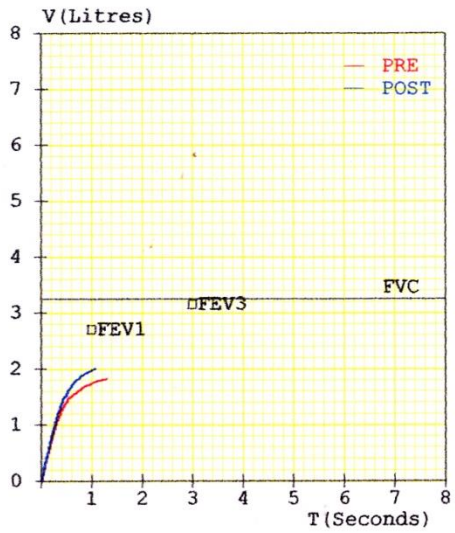
PULMONARY FUNCTION TEST - REPORT(Sample)

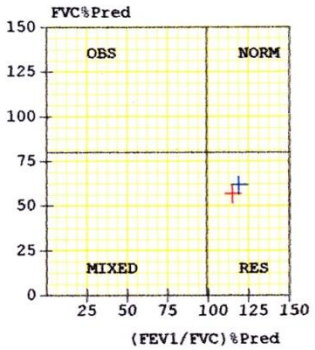
Sri Devaraj Urs Medical College, Tamaka ,Kolar

Department of Physiology, SDUMC campus,Tamaka, Kolar

Patient: Chowdappa		Age	: 37 Years	Sex	: Male
Refd. By:		Height	: 165 Cms	Smoker	: No
Pred.Eqns: USER 2		Weight	: 47 Kgs	Eth. Corr:	100
Date : 01/04/2010	ID: 582108	BSA	: 1.5 m2	Temp :	30 degrees







FVC Results

Parameter		M.Pred	Pre	%Pred	M.Post	%Pred	%Imp
FVC	(L)	03.24	01.85	057	02.02	062	+09
FIVC	(L)	-----	-----	---	-----	---	+00
FEV.5	(L)	-----	01.41	---	01.58	---	+12
FEV1	(L)	02.69	01.76	065	02.00	074	+14
FEV3	(L)	03.14	01.85	059	02.02	064	+09
PEFR	(L/s)	08.60	03.73	043	03.99	046	+07
PIFR	(L/s)	-----	-----	---	-----	---	+00
FEF25-75	(L/s)	03.98	02.62	066	02.98	075	+14
FEF75-85	(L/s)	-----	01.02	---	01.41	---	+38
FEF.2-1.2	(L/s)	06.84	03.14	046	03.51	051	+12
FEF 25%	(L/s)	07.76	03.73	048	03.98	051	+07
FEF 50%	(L/s)	05.58	02.96	053	03.17	057	+07
FEF 75%	(L/s)	02.77	01.41	051	01.85	067	+31
FEV.5/FVC	(%)	-----	76.22	---	78.22	---	+03
FEV1/FVC	(%)	83.02	95.14	115	99.01	119	+04
FEV3/FVC	(%)	96.91	100.00	103	100.00	103	+00
FVC Time	(Sec)	-----	01.29	---	01.07	---	---
ExplTime	(Sec)	-----	00.13	---	00.12	---	---

DOXOFYLLINE

Sl.No	PATIENT DETAILS				FEV_1		FVC		PEFR	
	O.P.NO.	AGE	SEX	SEVERITY	Pre	Post	Pre	Post	Pre	Post
1	402445	35	M	mild	83	88	91	78	60	60
2	503133	32	F	moderate	70	93	78	93	44	72
3	404435	36	M	moderate	63	88	80	106	31	22
4	466329	23	F	moderate	64	68	57	63	61	63
5	503536	35	F	moderate	60	78	48	69	61	68
6	549842	21	F	moderate	69	75	61	69	62	68
7	541206	37	F	moderate	75	85	65	76	66	65
8	558721	32	M	mild	92	102	82	92	74	83
9	566864	37	F	moderate	64	67	58	62	31	31
10	566863	39	M	moderate	65	76	58	65	55	67
11	582111	22	F	moderate	67	81	60	72	55	70
12	582092	39	F	moderate	77	92	65	78	53	63
13	582101	23	M	moderate	60	65	58	64	34	28
14	582106	39	F	moderate	73	86	62	75	42	61
15	582109	38	F	moderate	60	76	60	67	25	58

Sl.No	FEF 25%-75%		FEV_1/FVC		H.R.		S.BP.		D.BP.		R.R		ADR
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	
1	46	98	92	113	72	74	110	112	80	80	20	21	H
2	42	50	100	100	70	74	120	120	70	70	20	21	
3	27	39	78	83	68	68	110	110	70	72	20	20	H,N,Hb
4	58	61	111	107	70	71	100	100	70	74	19	18	
5	61	92	120	113	84	84	120	120	80	80	22	22	N
6	67	63	114	110	64	70	120	120	80	80	20	20	
7	67	61	116	111	82	80	110	110	80	80	21	21	
8	79	86	112	111	82	82	124	122	70	70	17	18	N
9	50	50	110	107	80	84	126	126	90	92	19	20	
10	58	72	112	116	82	83	118	120	86	86	18	18	H
11	70	74	112	111	78	78	120	122	70	70	20	20	
12	62	69	120	118	76	76	116	118	80	80	19	18	H
13	48	46	104	100	80	82	118	118	78	80	17	18	
14	69	76	117	114	78	80	118	120	82	82	20	20	N
15	35	64	100	114	80	82	120	120	78	80	18	18	

DOXOFYLLINE

Sl.No	PATIENT DETAILS				FEV_1		FVC		PEFR	
	O.P.NO.	AGE	SEX	SEVERITY	Pre	Post	Pre	Post	Pre	Post
16	582095	40	M	moderate	61	68	50	56	47	51
17	446160	36	M	moderate	71	90	56	71	47	49
18	585801	40	F	moderate	65	81	54	69	46	60
19	546960	29	M	moderate	70	89	52	70	49	55
20	599736	37	F	moderate	72	75	64	63	46	56
21	599766	21	F	moderate	72	79	67	75	56	65
22	533769	37	M	moderate	69	72	57	62	45	55
23	530562	38	M	moderate	71	79	59	67	54	69
24	592949	39	M	moderate	75	89	62	74	55	80
25	585689	36	M	moderate	71	80	59	66	56	71
26	562969	38	M	moderate	69	83	59	74	67	77
27	505739	32	M	moderate	65	71	56	63	53	57
28	599739	35	M	moderate	69	78	57	66	52	68
29	556108	30	F	moderate	75	90	66	82	73	73
30	614932	26	M	moderate	74	91	73	86	66	89

Sl.No	FEF 25%-75%		FEV_1/FVC		H.R.		S.BP.		D.BP.		R.R		ADR
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	
16	82	76	123	121	78	78	114	116	78	80	17	17	
17	83	98	128	127	72	74	110	112	80	80	20	21	H
18	86	79	121	117	70	72	120	120	80	84	20	19	
19	80	95	127	127	70	71	100	100	60	64	18	19	H
20	68	77	113	120	84	84	118	118	80	82	18	18	
21	60	55	107	105	78	78	122	122	84	84	17	17	
22	69	70	120	116	84	84	124	124	82	86	18	18	
23	92	89	121	118	80	82	120	122	84	88	17	18	H
24	84	105	120	121	74	74	114	116	82	82	18	17	
25	79	93	121	121	82	82	120	118	82	82	16	17	H
26	62	77	116	112	80	82	116	118	82	84	18	18	
27	80	70	116	114	78	80	122	122	84	82	19	19	
28	85	86	120	117	86	86	122	122	80	80	18	17	
29	81	89	115	109	78	80	110	108	74	76	16	17	H
30	44	64	102	104	80	82	106	108	74	80	17	17	N

AMINOPHYLLINE

Sl.No	PATIENT DETAILS				FEV_1		FVC		PEFR	
	O.P.NO.	AGE	SEX	SEVERITY	Pre	Post	Pre	Post	Pre	Post
1	400632	34	F	moderate	68	77	70	67	57	57
2	503535	21	F	moderate	72	75	72	71	62	68
3	503491	32	M	moderate	61	69	73	59	28	52
4	549846	32	F	moderate	61	65	73	73	28	52
5	559480	38	M	moderate	63	58	57	52	54	22
6	472049	21	F	moderate	63	61	58	57	53	62
7	558723	28	M	mild	87	91	80	83	75	79
8	566866	40	M	moderate	63	64	52	53	34	38
9	586443	26	F	moderate	73	75	67	69	59	64
10	582093	38	F	moderate	63	60	63	50	33	38
11	582094	25	M	moderate	63	60	54	58	56	40
12	582110	40	M	moderate	69	72	64	56	51	52
13	582105	20	F	mild	82	95	89	87	57	59
14	582108	37	M	moderate	65	74	57	62	43	46
15	585029	20	M	moderate	61	59	53	52	44	54

Sl.No	FEF 25%-75%		FEV-1/FVC		H.R.		S.BP.		D.BP.		R.R		ADR
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	
1	46	70	97	116	84	86	130	130	80	82	20	21	H, Hb
2	37	43	99	105	78	78	120	120	84	84	22	22	N
3	31	75	83	118	80	84	130	132	80	80	19	20	Hb
4	31	34	83	89	78	80	120	120	78	78	20	20	H,Hb
5	44	38	111	111	78	78	118	120	84	84	18	19	H
6	58	57	108	107	68	68	110	110	70	70	18	20	
7	64	63	109	109	80	82	130	132	80	80	23	25	
8	51	54	120	121	78	80	120	122	78	78	17	18	HN
9	64	65	109	109	82	82	118	120	74	74	18	19	H
10	39	50	100	121	74	76	124	124	82	80	20	20	N
11	69	38	115	103	76	76	126	128	88	88	19	21	
12	52	96	108	129	68	68	110	110	80	82	18	18	H
13	40	73	92	109	72	72	120	122	84	84	20	20	
14	66	75	115	119	84	84	120	120	80	80	18	19	
15	60	66	114	115	70	70	116	116	80	78	19	19	HN

AMINOPHYLLINE

Sl.No	PATIENT DETAILS				FEV_1		FVC		PEFR	
	O.P.NO.	AGE	SEX	SEVERITY	Pre	Post	Pre	Post	Pre	Post
16	583096	32	M	moderate	65	71	56	63	53	57
17	584457	39	M	moderate	72	79	62	77	54	46
18	599734	21	M	moderate	74	72	66	68	54	55
19	599733	40	M	mild	89	89	78	78	40	55
20	599773	27	F	mild	83	82	77	75	48	66
21	599769	25	F	moderate	80	83	73	76	41	64
22	508871	40	F	moderate	70	71	58	58	52	65
23	546930	35	F	moderate	71	78	60	68	62	65
24	560425	36	F	moderate	68	67	58	58	57	60
25	564621	36	M	moderate	63	67	52	58	51	69
26	568861	38	M	mild	87	87	78	78	40	55
27	542910	34	F	moderate	65	70	61	67	36	30
28	509791	32	M	moderate	65	69	57	60	45	60
29	551169	40	F	moderate	71	76	62	64	60	66
30	568914	35	F	moderate	69	70	65	60	37	54

Sl.No	FEF 25%-75%		FEV_1/ FVC		H.R.		S.BP.		D.BP.		R.R		ADR
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	
16	80	70	116	114	74	76	124	126	86	88	19	20	H
17	77	69	116	102	80	82	122	124	82	84	18	19	
18	73	63	113	107	74	76	120	122	78	78	17	18	H
19	71	73	114	114	80	82	114	116	78	78	18	18	N
20	61	61	108	109	80	80	122	124	82	82	18	19	
21	59	60	109	109	74	74	120	122	76	78	19	20	H,Hb
22	76	87	121	122	76	76	112	114	70	70	18	19	
23	85	81	120	114	70	72	120	118	74	76	17	18	H
24	84	78	118	115	78	80	116	116	74	76	18	19	
25	86	71	121	116	74	74	108	110	70	72	17	19	HN
26	69	71	113	113	84	86	122	122	80	82	18	20	H
27	54	52	107	104	82	83	112	114	80	80	18	21	
28	64	59	114	115	76	78	110	112	80	82	20	20	H, Hb
29	79	85	114	119	80	82	120	120	76	78	18	19	
30	52	72	107	116	82	84	118	120	84	84	17	19	H

KEY TO MASTER CHART

Sl.No – Serial Number

O.P.NO- Out Patient Number

FEV_1- Forced expiratory volume in 1 s

FVC- Forced vital capacity

PEFR -Peak expiratory flow rate

$FEF_{25\%-75\%}$- Forced Mid Expiratory Flow

H.R- Heart Rate

S.BP- Systolic Blood pressure

D.BP- Diastolic Blood pressure

R.R- Respiratory Rate

ADR- Adverse Drug Reactions

Pre- Pre medication

Post- Post medication

H- Headache

N- Nausea

Hb- Heart burn