EFFICACY, SAFETY AND COST EFFECTIVENESS OF ORAL DOXOFYLLINE AND THEOPHYLLINE FOR MILD TO MODERATE PERSISTENT BRONCHIAL ASTHMA: A RANDOMIZED PROSPECTIVE OPEN LABELED COMPARATIVE STUDY

Dissertation Submitted to

THE TAMILNADU DR. M.G.R. MEDICAL UNIVERSITY

In partial fulfilment of the

regulations for the award of the degree of

M.D. (PHARMACOLOGY)

BRANCH – VI

GOVT. CHENGALPATTU MEDICAL COLLEGE & HOSPITAL

THE TAMILNADU DR. M.G.R. MEDICAL UNIVERSITY

CHENNAI, INDIA.

APRIL 2016

CERTIFICATE

This to certify that this dissertation entitled, **"Efficacy, safety and cost effectiveness of oral Doxofylline and Theophylline for mild to moderate persistent bronchial asthma: A randomized prospective open labeled comparative study''** by the candidate Dr.M.Nandhini Priya for M.D (Pharmacology) is a bonafide record of the research work done by her, under the guidance of **Dr.S.Purushothaman,MD.,** Professor, Department of Pharmacology, Chengalpattu Medical College, during the period of study (2013-2016), in the Department of Pharmacology, Chengalpattu Medical College, Chengalpattu - 603001. I also certify that this dissertation is the result of the independent work on the part of the candidate.

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CERTIFICATE

This is to certify that the dissertation entitled, **"Efficacy, safety and cost effectiveness of oral Doxofylline and Theophylline for mild to moderate persistent bronchial asthma: A randomized prospective open labeled comparative study"** submitted by the candidate Dr.M.Nandhini Priya in partial fulfilment for the award of the degree of Doctor of Medicine in Pharmacology by The Tamilnadu Dr.M.G.R. Medical University, Chennai is a bonafide record of original work done by her under my guidance and supervision in the Department of Pharmacology, Chengalpattu Medical College, Chengalpattu during the academic year 2013-16.

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DECLARATION

I Dr.M.Nandhini Priya, solemnly declare that the dissertation titled **"Efficacy, safety and cost effectiveness of oral Doxofylline and Theophylline for mild to moderate persistent bronchial asthma: A randomized prospective open labeled comparative study''** has been done by me, in the Department of Pharmacology, Chengalpattu Medical College, Chengalpattu under the guidance of **Dr.S.Purushothaman,MD.,** Professor, Department of Pharmacology, Chengalpattu Medical College, Chengalpattu. This dissertation is submitted to The Tamilnadu Dr. M.G.R. Medical University, Chennai, in partial fulfilment of the rules and regulations for the award of M.D degree branch VI (pharmacology) to be held in April 2016. I also declare that this bonafide work was not submitted by me on any previous occasion for the award of any degree or diploma to any other university.

Place: Chengalpattu

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Signature of the Candidate

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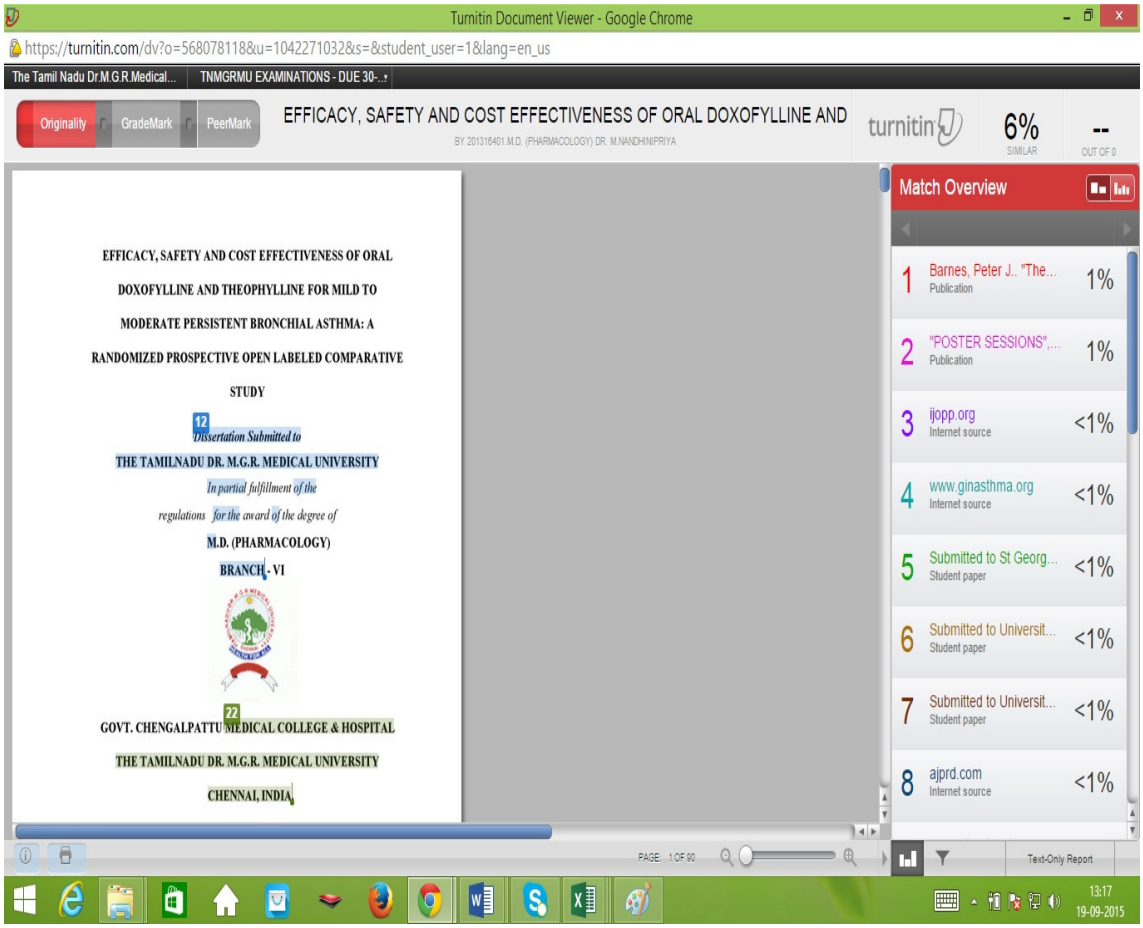

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1

CONTENTS

LIST OF FIGURES

LIST OF TABLES

ABBREVIATIONS

Ach	-	Acetylcholine
ACOS	-	Asthma – COPD Overlap Syndrome
AUC	-	Area Under the Curve
cAMP	-	Cyclic Adenosine Mono Phosphate
CCR	-	Chemokine receptor
CGRP	-	Calcitonin Gene Related Peptide
COPD	-	Chronic Obstructive Pulmonary Disease
CTZ	-	Chemoreceptor Trigger Zone
Cyp450	-	Cytochrome P 450
FEV_1	-	Forced Expiratory Volume in one second
FGF	-	Fibroblast Growth Factor
FVC	-	Forced Vital Capacity
GM – CSF	-	Granulocyte, Monocyte Colony Stimulating Factor
HDAC	-	Histone deacetylase
HLA	-	Human Leukocyte Antigen
ICS	-	Inhaled Corticosteroid
IgE	-	Immunoglobulin E
IGF	-	Insulin like Growth Factors
IL	-	Interleukin
KGF	-	Keratinocyte Growth Factor
LABA	-	Long Acting Bronchodilator
LT	-	Leukotriene

MMEF	-	Maximum Mid Expiratory Flow Rate
NANC	-	Nonadrenergic, noncholinergic nerves
NF-KB	-	Nuclear factor K Beta
NK	-	Neurokinin
PAF	-	Platelet activating factor
PDGF	-	Platelet Derived Growth Factor
PEFR	-	Peak Expiratory Flow Rate
PI3K	-	Phospo Inositol 3 Kinase
TGF	-	Transforming Growth Factors
VEGF	-	Vascular Endothelial Growth Factor

ABSTRACT

AIM :

To compare the efficacy, safety and cost effectiveness of oral Doxofylline and Theophylline for mild to moderate persistent bronchial asthma patients.

MATERIALS AND METHODS:

A Randomized prospective, open labeled comparative study of 1 year (Jul2014-Jun2015) duration was conducted in 186 patients who were attending the thoracic medicine outpatient department of Chengalpattu Medical College satisfying the inclusion and exclusion criteria after obtaining ethical clearance.

METHODOLOGY:

The study subjects were randomly allocated into two groups. Group 1 patients were treated with Doxofylline 400mg once daily and group 2 patients were treated with Theophylline twice daily. Demographic data, history, clinical examination and details of drug prescription by the treating physician were recorded in the study proforma. Relevant lab investigations were done at the beginning and at the end of the study. The patients were followed up for 12 weeks. The schedule of patient visit is as follows Visit 1 for initial or baseline assessment and follow-up at 4, 8 & 12 weeks.

STATISTICAL ANALYSIS:

The data collected were analyzed using Student t test (two tailed, independent) to find the significance of study parameters on continuous scale between two groups. Chi-square/ Fisher Exact test was used to find the significance of study parameters on categorical scale between two or more groups.

RESULT:

Doxofylline was better than deriphylline in subjective parameters of asthma control test questionnaire and subjective rating of asthma control. Doxofylline had equal efficacy as that of deriphylline in spirometric parameters ($p \leq 0.001$). Doxofylline was significantly safe compared to deriphylline as inferred from lesser incidence of adverse drug reactions. Adverse reactions are encountered in 10% of doxofylline and 22% of deriphylline group. Deriphylline was the cheaper and cost effective methylxanthene for the treatment of bronchial asthma in developing countries at population level. Doxofylline even though costlier had better safety profile with less adverse reactions compared to deriphylline. It can be used as an individual based approach in asthma management.

CONCLUSION:

Doxofylline is a newer methylxanthine with few adverse effects and equal efficacy as compared with deriphylline. It is a better alternative in the management of bronchial asthma.

KEY WORDS:

Bronchial Asthma, Methylxanthene, Doxofylline, Deriphylline, Efficacy, Safety, Cost Effectiveness.

INTRODUCTION

Asthma is a heterogeneous disease usually characterized by chronic airway inflammation .It is defined by the history of respiratory symptoms such as wheeze, shortness of breath, chest tightness and cough that vary over in time and intensity, together with variable respiratory airflow limitation.[1, 2]

The prevalence of asthma is 1-18%[1] in the world. It contributes 1% of the total disease burden of the world[3]. Genetic factors, allergens, infection, occupational exposure, smoking and air pollution trigger the development of bronchial asthma.

Treatment of asthma is directed towards the control of symptoms and bringing down the frequency of acute attacks with fewer side effects. It also aims to minimize remodeling of airways.

The drugs available for asthma are categorized as controllers, relievers and add on therapies. Controllers are used to bring down inflammation in airways, decrease the symptoms and minimize acute attacks. These include steroids by both inhalational and systemic route, leukotriene receptor antagonist, methylxanthines and anti IgE antibody. Relievers are used to relieve symptoms whenever needed. Relievers also play a role in preventing exercise induced asthma. Short acting β*2* agonists, anticholinergics in inhaled route, and theophylline are used as reliever medications. When the patient's symptoms persist even with adequate management , add on therapies are

used. Tiotropium, anti IgE antibody , Leukotriene receptor antagonist are given as add on therapy.[1, 2]

Methylxanthines are phosphodiesterase inhibitors. Theophylline is a widely used drug belonging to this group. It has bronchodilatory, anti-inflammatory, mucoregulatory, immune modulatory steroid sparing properties. It has a narrow therapeutic index with cardiac, gastrointestinal and CNS side effects which contribute non adherence to treatment[6, 7].

Doxofylline , another methylxanthine has fewer side effects and bronchodilation comparable to theopylline. They provide better asthmatic control and decrease the frequency of acute attacks[7]. As the prevention and management of asthma depends more on pharmacotherapy, there is a quest for bronchodilatory medications with few adverse effects. Methylxanthines are the first line of drugs for management of mild to moderate bronchial asthma as per Cochrane group[7].

For choosing among the asthma treatment options at population-level, pharmaco- economics plays an absolute role. Cost effectiveness analysis considers the cost of medications, effectiveness of the treatment, safety data and serves to adapt the best choice for the patients. This study is focused to compare the efficacy, safety and cost effectiveness of Doxofylline over Theophylline in mild to moderate persistent bronchial asthma patients.

Aims and Objectives

AIM & OBJECTIVES

- To compare the efficacy of oral Doxofylline and Theophylline for mild to moderate persistent bronchial asthma patients.

- To understand the safety profile of Doxofylline and Theophylline.

- To analyse the cost effectiveness of Doxofylline over Theophylline.

Review Of Literature

REVIEW OF LITERATURE

HISTORY:

The word "ASTHMA" is derived from Greek which means a condition involving difficulty in breathing. British adapted "ASMA" from Greek which means "ASTMA"and then the final form "ASTHMA" evolved.

It was Hippocrates (460-370Bc) who noticed the constructive effect of "ASTHMA". According to him, the various causes for the onset of this disease were climate, level of moisture and occupation. He compared it with epilepsy and distinguished asthma by its nature of occurrence due to external influence.

Later Areatus (2-3 century) explained the two forms of asthma as

- a breathing difficulty caused by activities such as running
- a constructive breathing difficulty due to humidity and low temperature[8].

During the 12th century, the Egyptian physicians recommended the details of the patient's physical status, diet, hygiene, environment, personal attitude and behaviour pattern had to be known for better management of the disease. It was strongly believed that the mental condition of the patient will influence his physical well being[9].

More prime facts were unfolded in further studies. JEAN BAPTISTE VAN HELMONT (1577-1644) pointed out bronchi as the major throne of asthma. Osler explained the pattern of asthma as a result of dust inhalation and

fish intake[8]. Henry Hyde Salt, in his work, "On Asthma, its Pathology and Treatment"(1860), discriminated asthma from dyspnoea. He described the childhood asthma as a different form. The inhalation of dust, fur, hay etc. are other contributors towards the disease[9].

The definition of bronchial asthma given by the American Thoracic Society, New York in 1862 states that asthma is a hyper responsiveness of trachea and bronchi to multiple factors which result in airway narrowing of variable severity either spontaneously or due to therapy.

It was in the year 1900, adrenaline was identified as the drug for asthma. It relaxes smooth muscles of the respiratory tract. Regular use of adrenaline for asthma management came into practice. During 1906, the view of etiology of asthma as anaphylaxis and allergy was put forward.

From 1930, theophylline was used for asthma treatment. From 1967, the management included short acting β 2 agonist. In 1968, SIR JOHN FLOYER, through his work, "A TREATIES OF ASTHMA", brought forward the fact of bronchoconstriction. He pointed out different types of asthma like continuous, periodic and convulsive. He also stated that environmental factors provoke asthma.

The discovery of sodium chromoglycate in 1968 made a new path in this disease. Using inhaled steroids, anti-inflammatory effect was brought in the year 1972. In 1982, Nobel Prize was awarded for the discovery of slow reacting

substance, which played a role in mediating asthma. The discovery of Leukotriene receptor antagonist in 1990 helped in treating chronic asthma[9].

Omalizumab, anti-IgE antibody is a recombinant humanized monoclonal antibody[10]. It interrupts the reaction between IgE and inflammatory mediators, preventing crosslinking and degranulation.

EPIDEMIOLOGY

MAGNITUDE OF THE DISEASE:

Asthma is a major health hazard which affects the people of all age groups. The current asthmatic population is around 300 million worldwide[3]. In some geographical region, the prevalence exceeds 10% in adults and 30% in children. India harbours about 15-20 million asthmatics. The estimated prevalence of asthma in India is around 4% - 5% in adults and 10%-15% among pediatric population[12, 13] .In Tamilnadu, the prevalence is around 4.84%[13, 14]

THE SOCIO-ECONOMIC BURDEN:

As the global prevalence of asthma has an increasing trend, the socio-economic burden due to this illness is severe. It imparts a heavy blow on the society by decreasing in productivity, absenteeism in the work place, increase in hospitalisation, decrease in the longitivity of lives[15]. The direct and indirect costs for asthma care is evaluated and found to be more than that of TB/HIV AIDS management.

AETIOLOGY:

Asthma is multifunctional in origin .It arises from complex interaction of genetic and environmental factors. The airway inflammation seems to occur when genetically susceptible individuals are exposed to certain environmental factors .Additional environmental determinants are the concurrent exposure to cigarette smoke, atmospheric pollutants and respiratory tract infections[18].

THE FOLLOWING ARE THE RISK FACTORS:

- GEOGRAPHICAL DISTRIBUTION:

  Asthma is more widely distributed in the West compared to the other parts of the world.

- AGE AND SEX:

  Asthma is more commonly diagnosed during infancy. Childhood asthma occurs frequently in boys than girls; but in adults, the incidence reverses.

- ETHINICITY:

  The blacks have higher morbidity and mortality than whites due to asthma.

- SMOKING:

  Asthma occurs more often in children born to mothers who have smoking habit.

- AIR POLLUTION:

  Global warming increased concentration of harmful gases in air. Occupational exposure contributes to the rise in asthma prevalence.

- ATOPY AND ALLERGENS:

  Atopy is a major risk factor .Exposure to allergens in the early age of life is associated with higher incidence of asthma. Family history of any form of allergy and elevated IgE levels are more in favour of asthma[24].

- INFECTIONS AND INFESTATIONS:

  Few bacteria, viruses and parasites impart an increase in serum IgE level. (e.g.) Respiratory syncytial virus, Measles virus, Vaccine against pertussis[21].

- DIET

  Occurrence of allergy in the early life is reduced when the baby is breastfed. Obese individuals are more prone for asthma. Omega 3 fatty acid in the diet and antioxidants reduce the risk of asthma.

  Lot of stimuli, both constitutional and environmental are involved in bronchial asthma triggering.

The common triggers are the following:

- Allergens
- Drugs
- Occupational exposure
- Smoking
- Infections
- Stress
- Exercise associated

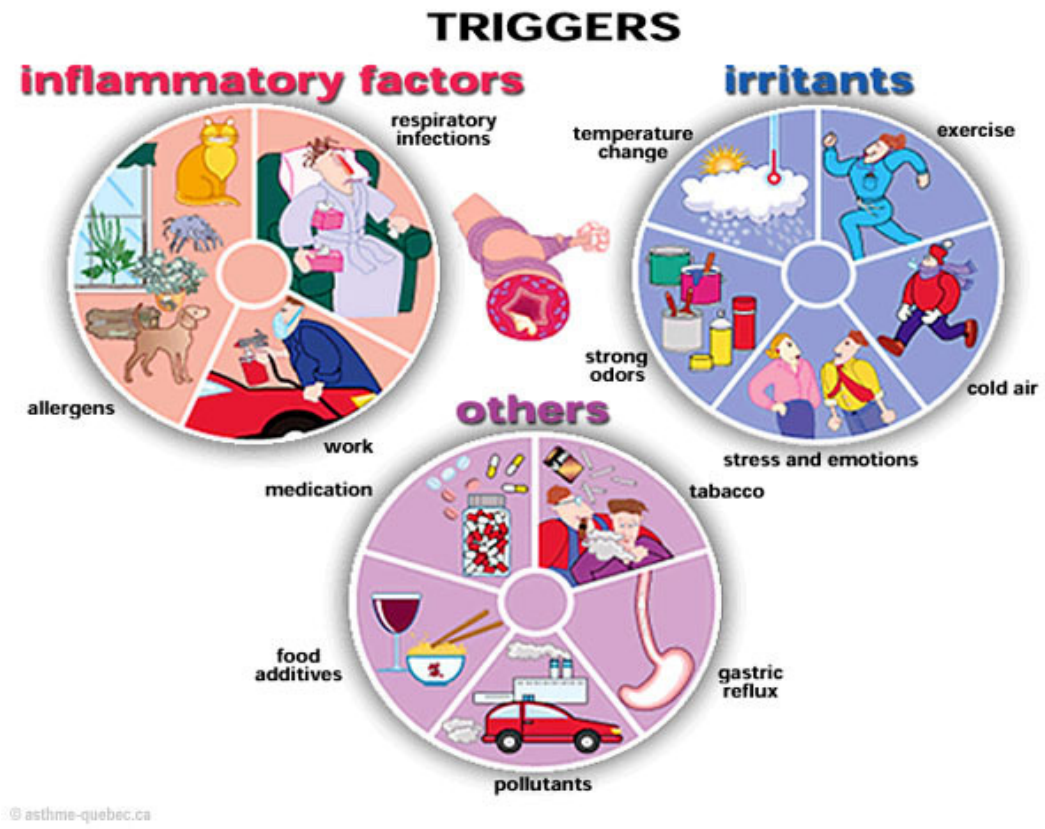


Figure 1: Triggers Of Asthma

ALLERGENS:

The following are the array of allergens which trigger the asthmatic attack: house dust mites, are found in high concentration in carpets, soft furnishings and bedding. Pet derived allergens are widespread in homes where dogs, cats or cattle are kept. Feathers also induce a kind of allergen. Fungal spores and antigens from cockroaches play an immense role in spreading allergens[19].

DRUGS:

Beta blocking drugs can induce bronchoconstriction in asthmatics. A small percentage of asthmatics develop bronchoconstriction when given

salicylates or non-steroidal anti-inflammatory drugs. These drugs block arachidonic acid metabolism down the prostaglandin pathway diverting it to the leukotriene pathway. Verapamil, piperazine, cimetidine also trigger asthma.

OCCUPATIONAL EXPOSURE:

Many agents encountered in the work place may induce asthma. The compounds include isocyanates, epoxyresins, persulphates, hardwood dusts, grain dust etc,.

ENVIRONMENTAL AND AIR POLLUTION:

Increasing prevalence of asthma is attributable to atmospheric pollution which plays a role in triggering exacerbations of pre-existing of asthma. Nitrogen dioxide, ozone, sulphur dioxide and airborne particulates have acute adverse effects on asthma during air pollution episodes[20]. Motor vehicle emissions, power stations, fuel burning industries, gas cookers, kerosene heaters, burning of fossil fuels, domestic coal burning, block smoke, pollens, allergens are particularly associated with asthma.

SMOKING:

Cigarette smoking is associated with increased levels of Ig E and with increased sensitization to certain occupational allergens in particular. Maternal smoking during pregnancy increases the risk of developing atopic disease in infancy. Passive exposure to cigarette smoke at home has an adverse effect on asthma and other respiratory diseases among children in particular.

INFECTIONS:

Many respiratory infections like influenzaA, mycoplasma pneumonia, Chlamydia pneumonia, respiratory syncytial virus etc. provide a transient increase in airway responsiveness in normal individuals and in asthmatics[21, 22].

EXCERSIE INDUCED:

Hyperventilation during exercise along with respiratory heat exchange and water loss provoke the occurrence of bronchoconstriction and bronchial asthma. The bronchoconstriction due to exercise depends on the strength of the stimulus and also on the quality of nonspecific airway responsiveness[23].

STRESS:

The emotional and cognitive factors induce the T helper cytokines. When the individual is provoked by a stimuli, inflammatory response is generated resulting in prolonged duration and more frequent severe asthmatic attack. The other mechanism suggested is vagal mediated response promoting bronchoconstriction.

CO-EXISTING DISORDERS:

There are few conditions which occur along with asthma. Management of these disorders are essential for better control of asthma.

1. RHINITIS AND SINUSITIS:

More than 50% of the asthmatics have co-existing rhinitis and sinusitis. Proper management of allergic rhinitis is important[25, 26].

2. GASTRO-OESOPHAGEAL REFLUX DISEASE:

GERD occurs in about 75% of asthma patients. The mechanism implicated are bronchoconstriction as a result of lower esophageal sensory stimulation and micro aspiration[27]. Treatment of GERD is essential.

3. OBESITY:

Obesity triggers the expression of inflammatory mediators responsible for airway constriction. Obesity is directly proportional to the rate of asthma occurrence[28].

PATHOGENESIS OFASTHMA:

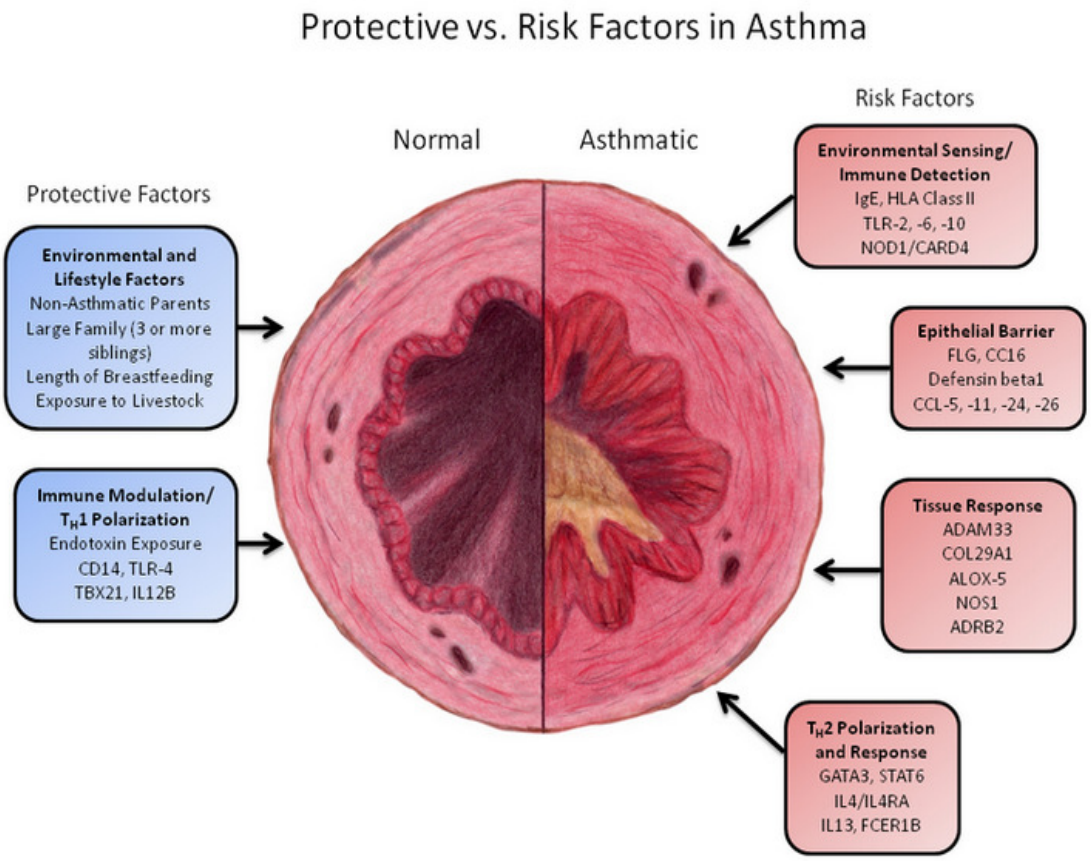


Figure 2: Pathogenesis Of Asthma

Asthma is a spectrum of disorders with airway inflammation along with hyper responsiveness resulting in airway obstruction. Proper understanding of its mechanism of development is necessary for its management.

GENETICS OF ATOPY AND ASTHMA:

There is strong evidence for the hereditary contribution to the etiology of asthma[24]. Asthma and atopy run in families. First degree relatives of asthmatics have a significantly higher prevalence of asthma than the relatives of non asthmatic patients.

Atopy is a constitutional tendency to produce significant amount of IgE on exposure to small antigens. Atopic individuals demonstrate positive reactions to antigens on skin prick test and have a high prevalence of asthma, allergic rhinitis, utricaria and eczema.

The genetic contribution to asthma is complex involving polygenic inheritance and genetic heterogeneity.

Asthma has an autosomal recessive inheritance with dominant and co-dominant expression. The below mentioned are some suggested polymorphisms seen in the genes of asthma patients: chromosome 5 has genes representing IgE, Interleukin 3, interleukin 4, interleukin 5, interleukin 9, interleukin 13 and GM-CSF which play a vital role in asthma.

Chromosome 2 encodes the atopy gene which is represented by FcER 1 region. FcER 1 is present on basophils, mast cells and dendritic cells. Its function is to increase the uptake of antigen and its expression.

Chromosome 12 provides a connection between asthma and atopy by the way of gamma interferon and nitric oxide production.

Chromosome 6 harbours the gene encoding HLA class II and cytokine TNF α. These are involved in the susceptibility and severity of asthma.

Chromosome 14 and 7 encodes the T cell receptor proteins which influence the IgE function[18].

BRONCHIAL HYPERRESONSIVENESS:

Most of the symptoms and signs of asthma are due to bronchial hyper responsiveness. There is an altered response in asthma patients compared with normal subjects to the external allergens. This response can be measured with the help of bronchial provocation test. There is a direct link among the severity of the disease, the need of the drugs and provocation concentration. This test measures the only one important component of asthma and serves as a tool for assessing asthma control[30].

INFLAMATORY CELLS EXPRESSED IN ASTHMA:

The range of cells associated with asthma include not only mast cells, eosinophils, cytokines, T – lymphocytes but also structural cells like epithelial cells, endothelial cells, smooth muscle cells and fibroblasts[32].

MAST CELLS:

Mast cells are seen on entire respiratory tract. They are clustered in the sub mucosal and epithelial surface of the bronchi. Mast cells release a cascade of preformed mediators as well as produce new mediators in a time interval of 30 minutes. Histamine, mast cells proteases particularly tryptase, newly formed mediators like prostaglandin D2, leukotriens, cytokines IL 4, IL5, IL6 and TNF α which are contributed by mast cells form the central mechanism[34].

BASOPHILS:

The only other cells to secrete histamine are basophils. Basophils can be triggered not only by Ig E mediated factors but also other substances such as IL 1, IL -3, IL – 8, RANTES, PAF etc. Their sensitivity to anti IgE is 100 times higher than that of mast cells. Basophils produce LTC 4, and they contribute more to the allergies occurring in skin[32].

EOSINOPHILS:

Eosinophilia particularly in the airway mucosa is linked with the diagnosis of asthma. Their count correlates with the disease activity. The granules present in the eosinophils such as eosinophil cationic protein, major basic protein, eosinophil peroxidase, eosinophil derived neurotoxin contribute to

the cytotoxic action of eosinophils. Eosinophils are the generators of oxygen free radicals, sulphidopentide, leukotrienes lineage of cytokines which induce bronchospasms and inflammation[36].

NEUTROPHILS:

Infiltration of neutrophils in the airways are observed in patients having severe asthma and those exposed to ozone and sulphur dioxide and also smokers. Their role in causing asthma or contributing to the disease severity is not clear[19].

MONOCYTES AND MACROPHAGES

These are the major cell types present in bronchial lumen. They have low affinity IgE Fc receptors which contribute to the release of mediators. They have significant role in atopic asthma.[38]

DENDRITIC CELLS

Dendritic cells have MHC class II molecules and they serve as prime antigen presenting cells in the airways. They induce T- Cell differentiation and Th 2 cytokine formation and the cascade of inflammatory events occur.[37]

LYMPHOCYTES

There are more number of T lymphocytes in asthma than B lymphocytes. Ig E mediated cellular activities in asthma rely upon T – cell activation. The activated T cells also regulate mast cells, eosinophils, epithelial cells and fibroblasts. The T lymphocytes are divided into CD4+ CD8+ Cells. The CD 4 + are also called as helper cells, which are further classified in to Th1 and Th2.

The Th 2 cells play a vital role in triggering IgE mediated inflammatory reactions, while Th1 inhibit IgE and have an opposite effect.[33]

AIRWAY SMOOTH MUSCLE CELLS

The smooth muscle cells of air passages are contracted in response to inflammatory mediators. The other events that occur as a consequence of inflammation are activation, proliferation, hypertrophy of the smooth muscle cells.[34]

EPITHELIAL CELLS

The epithelial cells participate in the inflammatory process and this induces damage to the epithelium. The repair of this event which is abnormal in the most of the asthmatic individuals, further contribute to the obstruction of airways.[39]

NEURAL MECHANISM OF ASTHMA

There exists an inter relationship between the inflammatory pathways and the neuronal aspects of airway function. The mediators of inflammation modulate the effect of neural tissues. On the other hand, the neuro transmitters influence the process of inflammation.

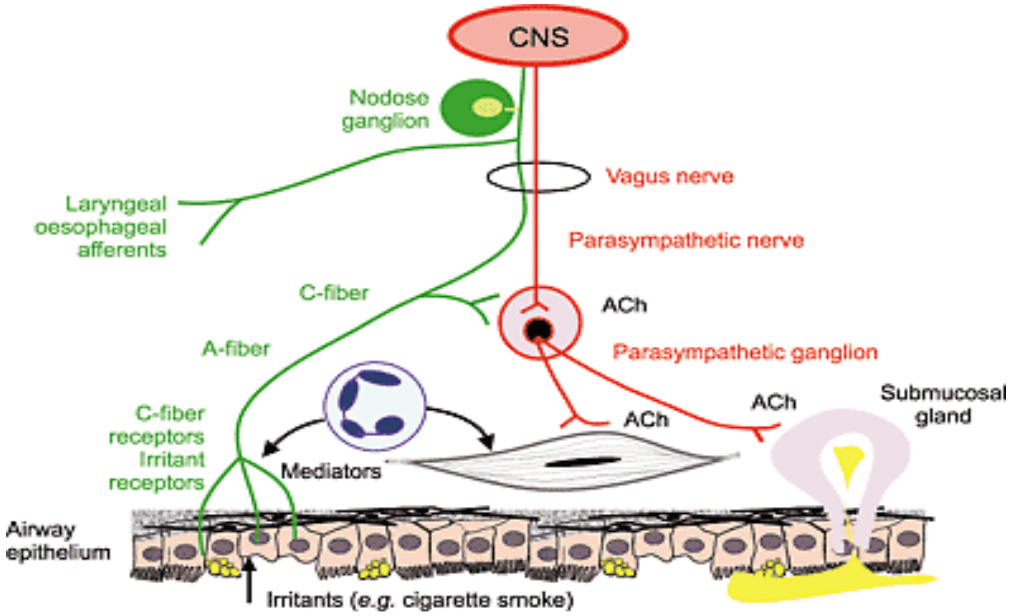


Figure 3: Neural Networks In Asthma

Cholinergic, adrenergic, NANC neural networks exert their control over airways. The cholinergic control of respiration is exerted through:

1. Increased vagal tone
2. Triggering of airway sensory receptors resulting in reflex bronchoconstriction.
3. Enhanced acetylcholine release from parasympathetic ganglia as well as post ganglionic neurons.

Adrenergic system exerts its effects through sympathetic nerves via α and β receptors. These nerves indirectly control cholinergic transmission through the prejunctional α or β receptors. Adrenergic influence is vital in exercise induced asthma and when asthma is triggered by cold air. The non adrenergic, non cholinergic nerves (NANC) are believed to release vasoactive intestinal peptide and nitric oxide. These neuro transmitters counteract the bronchial smooth muscles contractions mediated by acetyl choline. There is evidence that

inflammatory cells release superoxide which degrade VIP. This contributes to increased bronchial contraction.[29, 31]

AIRWAY NEUROPEPTIDES:

The sensory nerve fibres (C) which are unmyelinated are present in the airway.

They harbour various neuropeptides like substance P, neurokinin (NK), calcitonin gene related peptide (CGRP)

Due to the damage of the airway epithelium in asthma, the sensory nerve endings are exposed which may trigger the release of this neuro transmitters and result in the airway inflammation.[32]

AIRWAY REMODELLING:

Due to chronic inflammation and structural changes occur in the airway of asthmatics, these changes are referred as airway remodelling.

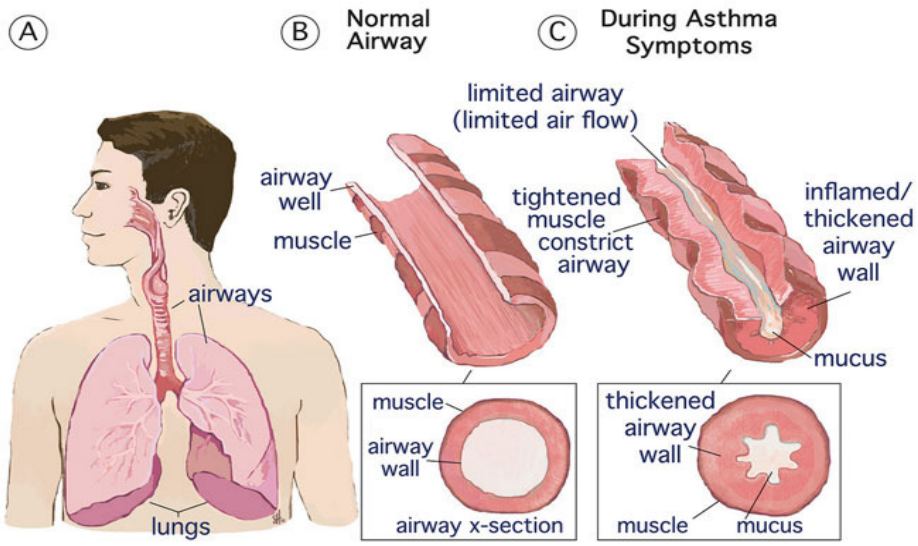


Figure 4: Airway Remodelling

GROWTH FACTORS IMPLICATED IN AIRWAY REMODELLING:

The damaged airway epithelial cells produce many growth factors such as transforming growth factors (TGF) α, β endothelin (ET). Insulin like growth factor (IGF) basic fibroblast growth factor b (FGF), platelet derived growth factor (PDGF).The activated fibroblast release connective tissue growth factor (CTDGF), vascular endothelial growth factor (VEGF), Keratinocyte growth factor (KGF) etc. which play a role in airway remodelling.[31]

CONSEQUENCE OF AIRWAY REMODELLING:

Airway remodelling, which involves all the layers of airway wall results in the following modifications:

1. Increasing in sloughing of the epithelium, leading to loss of integrity.
2. Exposure of the nerve endings.
3. Hypertrophy and hyperplasia of airway smooth muscles.
4. Destruction of Elastic tissues.
5. Increase in the number of blood vessels in the mucosa.
6. Micro vascular leakage.
7. Sub mucosal edema of the airways.
8. Mucus hyper secretion muscle plugs.

PATHOLOGY

The main pathology involved in asthma is airway thickening and remodelling which leads to narrowing of the airway lumen.[30] Apart from constriction of airways, bronchial congestion and edema are seen in the asthmatic. In chronic asthma there is inflammatory cells infiltration. Eosinophilia is consistently seen in asthmatic which is triggered by T – helper cells (CD4+). The role of mast cells are evident in immediate type of hypersensitivity reaction in asthmatics.[34]

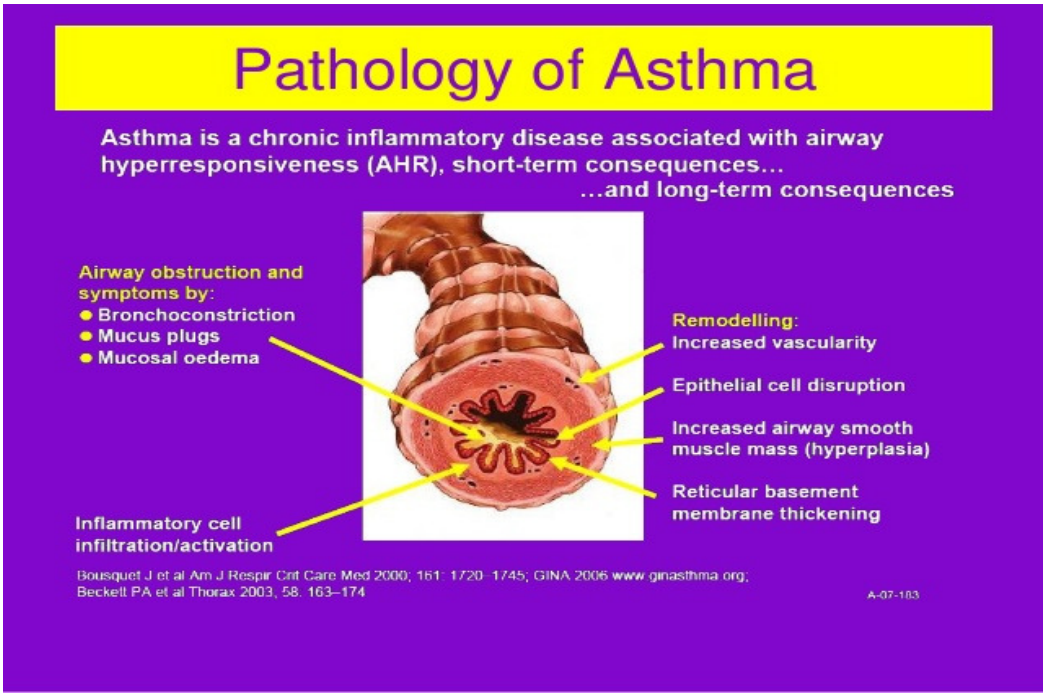


Figure 5: Pathology Of Asthma.

SPUTUM & BRONCHIO ALVEOLAR LAVAGE

The sputum and BAL in the asthma patient have the following features:

1. Cork screw shaped twists of condensed mucus (Curschmann's spirals)
2. Clusters of surface airway epithelial cells. (Creola bodies)

3. Eosinophils, metachromatic cells admixed with granule membrane lysophospholipase (Charcot – Leyden crystals)
4. Epithelial cells sloughing, eosinophilic cationic protein, major basic protein.[30]

AIRWAY PLUGGING

These are the result of mucus production by enlarged sub mucosal glands, mixed with inflammatory exudate, arranged in concentric lamellae. These plugs block the lumen of airways in asthmatics.

HISTOLOGICAL APPEARANCE

The mucosa of the airway in asthmatics show loss of integrity of epithelial surface, thickening of the basement membrane, mucosal infiltration with eosinophils, lymphocytes, smooth muscle hypertrophy. There is also dilatation of bronchial mucosal blood vessels as well as angiogenesis.[32]

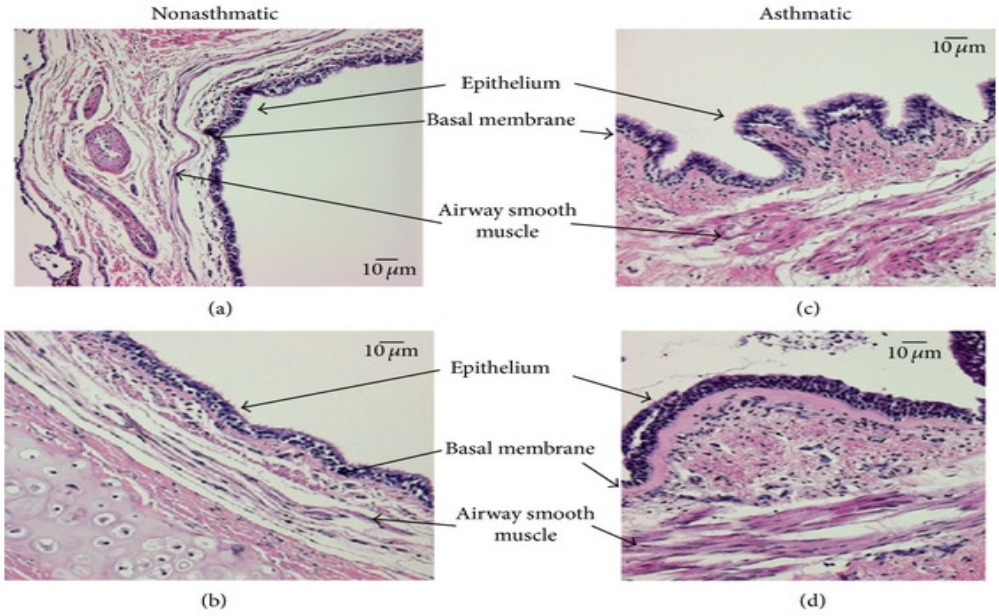


Figure 6: Mucosa Of The Airway In Asthmatics

DIAGNOSIS

HISTORY

- Abrupt onset of symptoms
- Variable in time and intensity
- More at Night
- Exaggerated by laughing, walking, allergens and low temperature
- Exacerbate with respiratory infection
- Changes in symptoms according to seasons
- Family history asthma, allergy or atopy.

SYMPTOMS

The symptoms vary with time, intensity or disappear during symptom free intervals.

- Wheeze
- Chest tightness
- Cough
- Shortness of breath.

FINDINGS ON PHYSICAL EXAMINATIONS

- Breath sounds with prolonged expiration
- Increased respiratory rate
- Orthopnoea
- Chest constriction
- Polyphonic, high pitched wheeze, maybe inspiratory, expiratory or both.
- In near fatal asthma, chest maybe silent

PULMONARY FUNCTION TEST

1. SPIROMETRY

Spirometry is the measure of airflow and lung volumes during a forced expiratory manoeuvre from full inspiration. It is fundamental to the diagnosis and assessment of airway disease. The measurements made during spirometry are referred as `dynamic lung volumes'. Spirometry provides three basic measurements.

- Forced vital capacity
- The forced expiratory volume in one second.
- The ratio of FEV1/FVC.

Airway obstruction is established by a decrease in FEV, out of proportion to the decrease in vital capacity (VC).This imparts a reduction in FEV1/FVC ratio. The maximum mid expiratory flow (MMEF) represents the airflow in the medium and small airways (FEF 25-75%).It may indicate mild airway disease.

Confirmation of asthma in spirometry is by establishing bronchoconstriction as evidenced by FEV1/FVC<70% and an improvement of >15% or 200ml in FEV1, 15 min after giving short acting beta 2 agonist by inhalation.[1, 40]

PEAK EXPIRATORY FLOW

This can be measured during spirometry or independently using a peak flow meter. Peak flow meter indicates only the greatest expiratory flow. It is used for monitoring the treatment. The two largest repeated measurements with variation within 5% is acceptable. The PEFR measurements are evaluated by comparing with the same person's best value, which is obtained during symptom free period. It has diurnal variation, being lowest in early morning.

The meters used by the patients at home have a zonal system with colour code for better interpretation. The PEFR of 80%-100% of the patient's best value is indicated by green zone, 60%-80% by yellow zone, below 60% by red zone. Red zone warns immediate medical care.[1]

LUNG VOLUMES

The changes occuring in lung volumes and capacities of the asthmatic patients are:

1. Increased total lung volume
2. Increased functional residual capacity

BRONCHIAL PROVOCATION TEST:

This is used in adult patients who do not have limitation of airflow at the time of assessment. Airway hyper responsiveness in such patients is demonstrated by bronchial provocation with methacholine or histamine. A decrease in FEV1 $\geq$ 20% from baseline is considered as bronchial asthma. The

specificity of this test is low as it can give false positive results in patients with other diseases.[40,42]

TYPICAL CHARACTERISTICS OF ASTHMA, COPD, AND ACOS

(Asthma-COPD overlap syndrome) [1]

FEATURE	ASTHMA	COPD	ACOS
Age	Any age Early onset	Rare < 35 yrs.	Usually >40 year History of symptoms present at early age.
Occurrence	Variable Aggravating factors present	Persistent symptoms Prolonged course	Persistent symptoms Prominent variability
Lung function	Variable airflow limitation, normal between symptoms	Post bronchodilator FEV1/FVC < 0.7	Not fully reversible
History	Mostly family/ personal history of allergy/ asthma present	History of exposure to noxious substance present	History of asthma, exposure to noxious substance present
Disease course	Improve after treatment	Progressive	Improve after treatment, Progressive
Chest X ray	Usually within normal limits	Changes suggestive of COPD present	Same as COPD
Airway pathology	Presence of eosinophils and/or neutrophils	Neutrophils in sputum, may have systemic inflammation	Eosinophils and/or neutrophils in sputum

Table 1: Characteristics Of Asthma, COPD And ACOS

FLOW-CHART FOR DIAGNOSIS OF BRONCHIAL ASTHMA[42, 1]

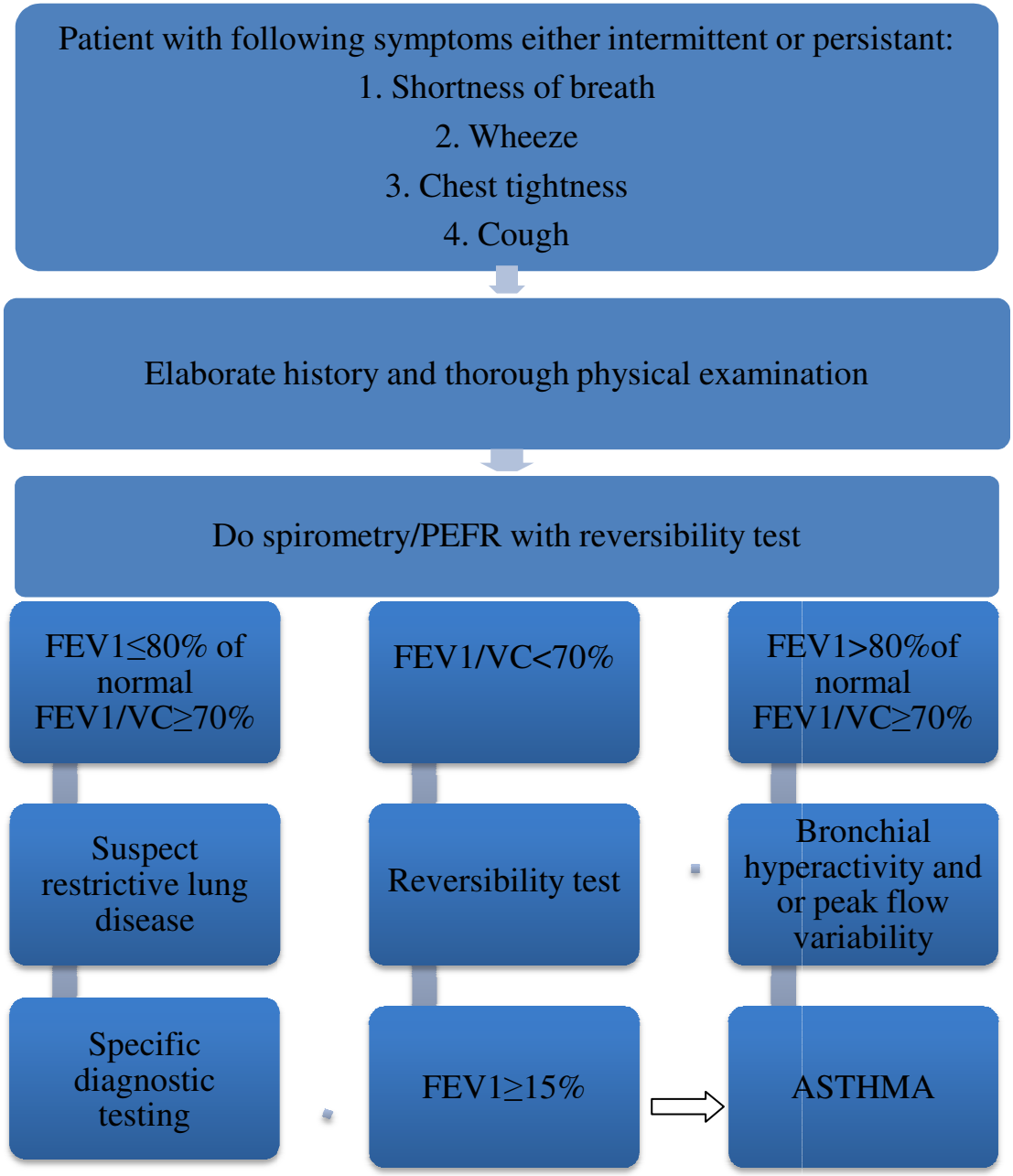


Figure:7 Flow-chart For Diagnosis of Bronchial Asthma

CLASSIFICATION OF BRONCHIAL ASTHMA:

1. ACCORDING TO THE LEVEL OF CONTROL[42]:

SYMPTOMS AND SIGNS	CONTROLLED	PARTLY CONTROLLED	UNCONTROLLED
1.Daytime symptoms	Nil or <2times/week	≥2times/week	
2.Activity limitation	Nil	Present	3/more feature of partly controlled asthma
3.Night waking due to asthma	Nil	Present	3/more feature of partly controlled asthma
4.Need for reliever medication	Nil or <2times/week	>2times/week	
5.Lung function PEF/FEV1	Normal	<80% predicted	

Table 2: Classification Of Bronchial Asthma

2. IN ACCORDANCE WITH THE CLINICAL SEVERITY:

(i). MILD ASTHMA

It is a well controlled asthma. It is treated with reliever medications or with low intensity controller medications as and when needed basis. The spirometry value of FEV1 is 60-80% of the predicted value.

(ii) MODERATE ASTHMA

These patients also have well controlled symptoms but with low dose ICS/LABA. Moderate asthma correlates with the FEV1 of 40-60% of the predicted value.

(iii) SEVERE ASTHMA

Patients in this state, need high dose ICS/LABA to control the symptoms. It may remain uncontrolled even with this treatment.

In severe obstruction, the FEV1 value will be <40% of the predicted.[40]

PRIMARY PREVENTION

Focus is laid on environmental triggers of asthma and its evidence. Priority to the reduction of exposure to occupational allergens helps in decreasing the incidence of asthma. The main of aim primary prevention is to protect the children from developing asthma. Few ways of achieving this are avoidance of maternal smoking, promoting breast feeding and avoidance of allergens. For obese individuals weight loss is advised.[41, 43]

ASTHMA - INFORMATION EDUCATION AND COMMUNICATION:

Effective asthma management depends on the patients and parents of paediatric patients' knowledge and understanding of asthma. Health education should begin as early as the diagnosis is made and should continue at each visit to hospital.

Healthcare providers should impart knowledge about the multifactorial nature of the disease and teach the patients about the practical skills needed for its better management.

Importance has to be laid on the identification and avoidance of precipitating factors, adherence to treatment and understanding the difference between reliever and preventer drugs.

Special attention is given for the technique of using inhaler devices and peak flow meter. They are educated to appreciate the day to day variability in peak expiratory flow rate and its role in recognising the influence of precipitating factors, their effect on disease process and in monitoring the treatment.

The healthcare provider should have good communication skill. Then only the needed information can reach to the patient. For this they should have a friendly nature and allow the patients to express their problems, beliefs and concerns. Besides being attentive, they have to impart appropriate information, reassure and encourage the patients. Hence good communication has a great impact on health literacy. The information should be in simple words with illustrations, pictures, drawing, etc. Patient's understanding can be confirmed by asking to repeat the important points. It means the patients clear understanding and the freedom to put forward their doubt.[1,42]

AVOIDANCE OF PROVOKING FACTORS:

Indoor allergens like house dust mite prevalence can be reduced by frequent dusting, vacuum cleaning and covering the carpet and mattresses etc.

Exposure to pet allergens should be avoided. Cigarette smoking both active and passive has to be abstained. Occupations and hobbies that provoke asthma have to be evaded as well. Ingested food additives, food allergens which trigger asthma have also to be refrained. Furthermore, medications which cause bronchoconstriction like beta blockers, aspirin etc. are to be avoided.[1, 42]

PHARMACOTHERAPY OF BRONCHIAL ASTHMA

Various means of bronchial asthma treatment are:

1. To decrease airway inflammation and hyper responsiveness.
2. To prevent the bronchoconstriction effect of vagal nerve
    - Anti cholinergics
3. Dilatation of airway smooth muscles-
    - Sympathomimetics
    - Methylxanthines
4. Blocking the release of anti-inflammatory mediators-
    - Mast cell stabilizers
5. Antagonising the effect of already released mediators of inflammation
    - Leukotriene antagonists
    - Antihistamines
    - PAF antagonists
6. Blocking the circulating IgE-
    - Omalizumab

ANTIASTHMATIC DRUG CLASSIFICATION

1. BRONCHODILATORS

- Agonists of beta2 adrenergic receptors
- Anticholinergics
- Methylxanthines

2.LEUKOTRIENE RECEPTOR ANTAGONISTS

- Montelukast
- Zafirlukast
- Lipoxygenase inhibitor-zileuton

3. PREVENT DEGRANULATION OF MAST CELLS

- Sodium chromoglycate
- Ketotifen

4. CORTICOSTEROIDS

- Inhaled route: beclomethasone, dipropionate, budesonide, fluticasone, Propionate, flunisolide, ciclesonide
- Systemic route: Hydrocortisone, Prednisolone etc. [42]

The use of above mentioned drugs fall under two categories:

The 'relievers' and the 'controllers'. The relievers are bronchodilator drugs used on need basis. Controllers are anti-inflammatory drugs taken in daily basis for prolonged period to keep symptoms of asthma under control.[1, 42]

BETA 2 ADRENORECEPTOR AGONISTS:

These act on the beta2 receptors on bronchial smooth muscle resulting in bronchodilation. Beta2 agonists stimulate the G protein coupled receptors that result in activation of adenylcyclase and finally increase cAMP which cause smooth muscle relaxation. cAMP also decreases mediator release from mast cells. These agents inhibit microvascular leakage and increase mucociliary transport by increasing ciliary activity. [44]

Selective beta2 agonists are preferred agents for bronchial asthma. By inhalation route they are the fastest acting drug.

Salbutamol, pirbuterol and terbutaline are faster acting drugs by inhalational route. So they are used for aborting an attack of acute asthma. Owing to their short duration of action, they are not suitable for prophylaxis.

Salmeterol, formoterol, carmoterol, indacterol are long acting beta2 agonists. They are useful for prophylaxis of bronchial asthma.

Adverse reactions:

Prolonged use may lead to down regulation of beta receptors contributing to tolerance. Tremors, palpitation, decrease serum potassium concentration, restlessness are other side effects.[6]

METHYLXANTHINES:

This group includes caffeine, theophylline and theobromine. Methylxanthines act by blocking the adenosine receptor, increase cAMP, inhibition of phosphodiesterase enzyme. At higher doses, these drugs release calcium from sarcoplasmic reticulum in skeletal and cardiac muscles.

When given orally they have rapid absorption. Metabolism is via cyp450 isoenzymes in liver. This paves way for a multitude of drug interactions.[6]

Side effects:

As these drugs are CNS stimulant at toxic doses they result in tremors, delirium and convulsions. Vomiting occurs due to gastric irritation and CTZ stimulation. More over theophylline has a narrow therapeutic index which plays a central role in causing toxic symptoms. [6]

ANTICHOLINERGICS:

Cholinergic blockers are effective only if bronchoconstriction is due to cholinergic activity. These drugs cause mainly dilatation of large airways. These are less efficacious and slower acting bronchodilators than the sympathomimetics. [6]These drugs are more effective for COPD than bronchial asthma.

Ipratropium and tiotropium act as competitive antagonists of Ach receptors on bronchial smooth muscle. They act through M_3 receptors which are G Protein Coupled receptors.[44]These drugs are inhalational agents. The

duration of action of Ipratropium is 4-6hrs while that of tiotropium is 24hrs.Both are ionic drugs that are poorly absorbed.[6, 29]

Side effects:

Dryness of mouth, nervousness, pharyngitis, headache, palpitation.

CORTICOSTEROIDS:

These drugs have potent anti-inflammatory and also decrease bronchial hyperactivity and mucosal edema. Anti-inflammatory action is due to decreased recruitment of inflammatory cells as well as decreased production of PG and LT. They block the mediators generated by arachidonic acid pathway.

Glucocorticoid bind to cytoplasmic receptors and the complex is transferred to the nucleus. These GR-drug complex binds to the nuclear response element present in the DNA. This results in up regulation transcription of anti-inflammatory factors. [45]

The primary indication of inhaled steroids is to decrease the inflammatory process. These drugs are used as maintenance therapy of chronic persistent asthma. Beclomethasone, dipropionate, Triamcinolone, Fluticasone, Budesonide, Mometasone are some of the agents used in inhalational route. Inhaled steroids are combined with long acting beta2 agonists and used as controller medication in bronchial asthma. [48]

Side effects:

The systemic therapy with glucocorticoids cause abnormalities in metabolism of carbohydrates, lipids, cushingoid features with salt and water retention, alteration in mood, osteoporosis, hypertension, cataract, immunosuppression etc. [46] Local effects like oropharyngeal candidiasis, dysphonia, pharyngitis are seen with inhaled steroid use.[47]

CROMOLYN LIKE DRUGS:

Sodium chromoglycate and nedocromil are the most common nonsteroidal antiasthmatic drugs used. They prevent degranulation of mast cells in response to allergic-non allergic stimuli .They are indicated only for prophylaxis of asthma. When used as inhalational agents they prevent bronchospasm and the cascade of further mediator release. Ketotifen has anti histaminic action apart from mast cell stabilizing property and is specially indicated for patients with multiple disorders like atopic dermatitis, perennial rhinitis, conjunctivitis etc. chromoglycan and nedocromil are often used in pediatric population as alternatives to inhale corticosteroids because of their safety profiles.[45]

Adverse reactions:

Local reactions like pharyngeal irritation, cough, reflex bronchospasm are observed .Headache, arthralgia, nasal congestion are rarely reported.

LIPOOXYGENASE INHIBITOR:

Zileuton inhibits the synthesis of LTB_4, LTC_4, LTD_4 from arachidonic acid. This results in blocking of chemotaxis and bronchoconstriction. This drug has short duration of action. It is used as controller in the management of bronchial asthma. [50]

Adverse reaction:

Nonspecific pain, headache, acid peptic disorder, elevated liver enzymes and hepatotoxicity.[51]

LEUKOTRIENE RECEPTOR ANTAGONIST:

Montelukast and zafirlukast inhibit the bronchoconstricting action of LTs at cys LT1 receptor.[51]They are selective antagonists of leukotriene receptors LTD_4 and LTE_4. By this action they inhibit bronchoconstriction, mucus secretion, vascular permeability and plasma exudation into the air way. Antileukotrienes are indicated in prevention of exercise, cold air, allergens and aspirin induced asthma.[51]

Adverse reactions:

Headache, nausea, abdominal pain, occasional elevation of liver enzymes are reported. Few cases of Churg Strauss syndrome is associated with their use.[51]

MONOCLONAL ANTIBODY-OMALIZUMAB:

Omalizumab is a monoclonal antibody against IgE. It blocks the reaction between IgE and mast cell / basophils .This inhibits the release of inflammatory mediators. It is indicated to prevent the attack of bronchial asthma in patients not responding to combination of long acting beta 2 agonist and a high dose of inhalational steroid. It is administered by subcutaneous route.

Adverse reactions:

Injection site reactions, viral, respiratory tract infections, headache, sinusitis and pharyngitis. [52]

MANAGEMENT OF ASTHMA

BASED ON PATIENT'S CONTROL OF ASTHMA SYMPTOMS:

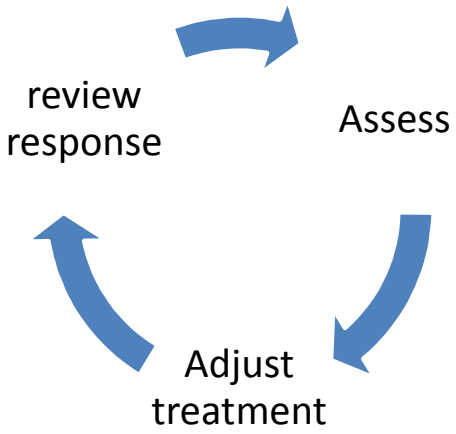


Figure 8: Control based asthma management cycle

Symptoms control serves as a tool for planning asthma management. The exceptions are severe asthmatics whose symptoms do not correlate with

responses or exacerbations .This approach of asthma management takes into account not only symptom control but also the future risk reduction. [42]

STEPPING DOWN AND STEPPING UP ASTHMA TREATMENT

Steps in asthma management

STEP1: Using reliever medication as and when needed basis.

STEP2: Continuous use of low dose controller medication added to step 1.

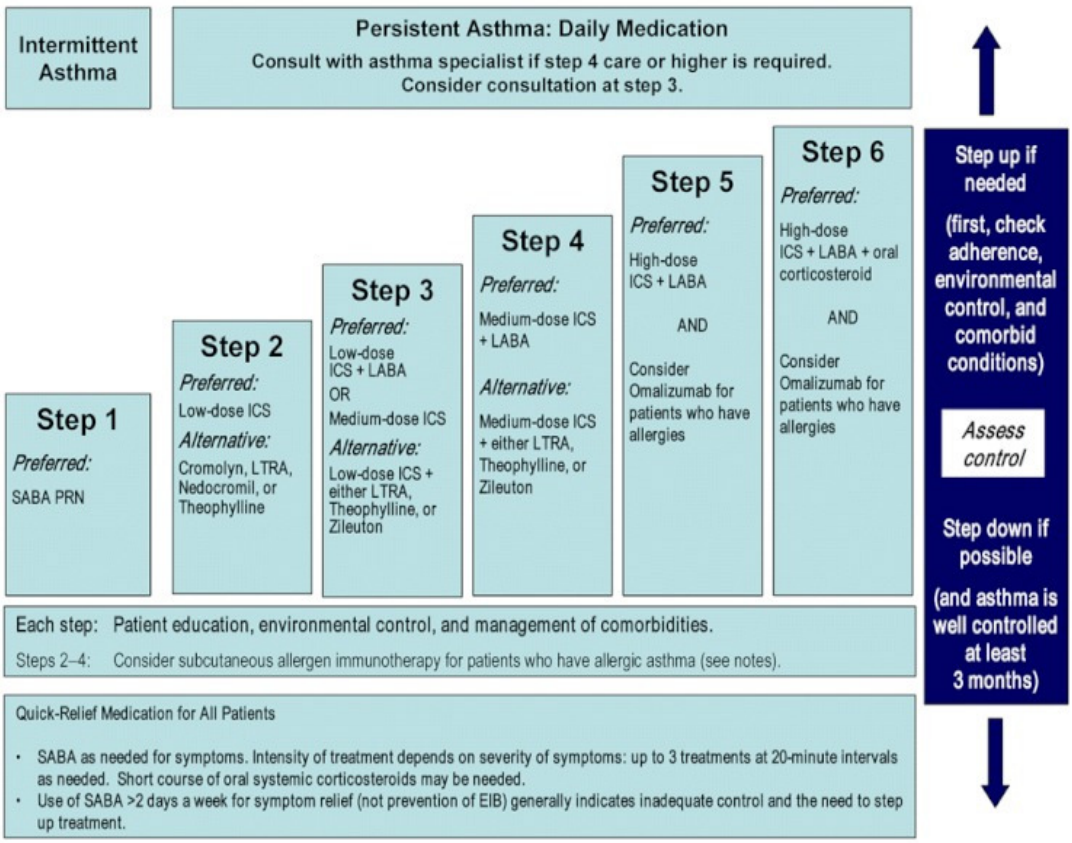
STEP3: Use of one or two controller medications along with step 1.

STEP4: Use two or more controller medications along with step 1.

STEP5: Tertiary care and / or add on medications.

Asthma patients should be followed up regularly and assessed for asthma control, adherence to medications, inhaler techniques etc.

If they do not respond to treatment then these step up treatment has to be given. If the asthma symptoms are well controlled and the lung function is stable for 3 or more months, then stepping down treatment may be considered.[1, 42]



— Key: **Alphabetical order is used when more than one treatment option is listed within either preferred or alternative therapy.** EIB, exercise-induced bronchospasm; ICS, inhaled corticosteroid; LABA, long-acting inhaled beta$_2$-agonist; LTRA, leukotriene receptor antagonist; SABA, inhaled short-acting beta$_2$-agonist

Figure 9: Step wise approach to control asthma symptoms and minimize future risk

DRUGS USED IN PRESENT STUDY

METHYLXANTHINE GROUP OF DRUGS:

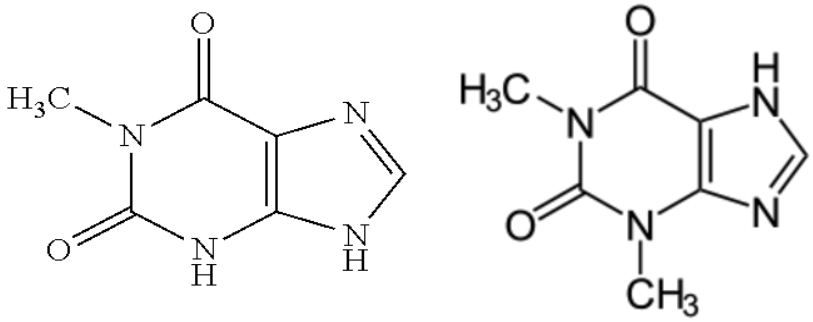
Methylxanthine is present in beverages like tea, coffee, cocoa. The CNS stimulant effect of these are attributed to methylxanthines. The major chemicals present are theophylline, theobromine and caffeine.

CHEMICAL STRUCTURE:

Theophylline is 1,3-dimethylxanthine

Theobromine is 3, 7-dimethylxanthine

Caffeine is 1, 3, 7-trimethylxanthine



1-Methylxanthine Theophylline

Figure 10: Structure Of Methylxanthine And Theophylline

MOLECULAR BASIS OF THEOPHYLLINE ACTION:

1. Phosphodiesterase inhibition.
2. Antagonism at adenosine A, A_2A, A_2B receptors.
3. Inhibition of nuclear factor K-β.
4. Inhibition of phospho-inositol-3 kinase δ.
5. Increased interleukin 10 secretion.
6. Enhanced apoptosis of inflammatory cells.
7. Decreased expression of ADP-ribose polymerase 1 which inhibits cell death.
8. Increased histone deacetylase activity.

PDE INHIBITION:

Theophylline is a nonselective inhibitor of phosphodiesterase. It acts on cyclic nucleotides, increases intracellular adenosine monophosphate (AMP) and cyclic 3'5' guanosine monophosphate (GMP) levels. Higher expression of

isoenzymes of PDE are encountered in bronchial asthma patients owing to its chronic inflammatory process or as a treatment outcome.[54]

ADENOSINE ANTAGONIST:

Theophylline inhibits A_1 and A_2 subtypes of adenosine receptors and is less potent against A3 receptors. It antagonises the bronchoconstricting effects of adenosine. [55]

INTERLEUKIN 10 RELEASE:

Interleukin 10 plays major role in anti-inflammatory actions. IL-10 concentrations are low in diseased states like asthma and COPD. IL-10 secretion enhanced by theophylline .[56]

EFFECTS OF GENE TRANSCRIPTION:

It decreases the expression of genes responsible for inflammation in asthma. This effect is mediated by blocking the translocation of nuclear factor KB(NF-KB)which is a proinflammatory transcription factor into the nucleus.[57]

EFFECTS ON KINASES:

Theophylline has direct inhibitory action on phosphoinositol 3 kinase, particularly the subtype P13K (P110) δ. This enzyme takes part in oxidative stress response. This property contributes to the theophylline's reversal action of corticosteroid resistance. This plays a major role in the management of severe asthma and COPD. [58]

EFFECTS ON APOPTOSIS:

Theophylline has the property of reducing apoptosis by virtue of its action on Bcl-2, an antiapoptic protein. This contributes to the inhibition of apoptosis in neutrophils.[59]

HISTONE DEACETYLASE ACTIVATION:

Acetylated and deacetylated state of histone determines the inflammatory gene expression. Bronchial asthma patients have increased expression of inflammatory genes as a result of histone acetylation and transcription.

This phenomenon is prevented by histone deacetylases (HDAC) which acts on the promoter site present in the nucleus. Corticosteroids inhibit the inflammatory process by the activation of histone deacetylase, thus suppressing the expression of inflammatory genes. [(61)] This process is defective in COPD patients causing reduced expression of HDAC2 and contributing to steroid resistance in COPD. This defect is also encountered in severe asthmatic patients who have the habit of smoking. [62]

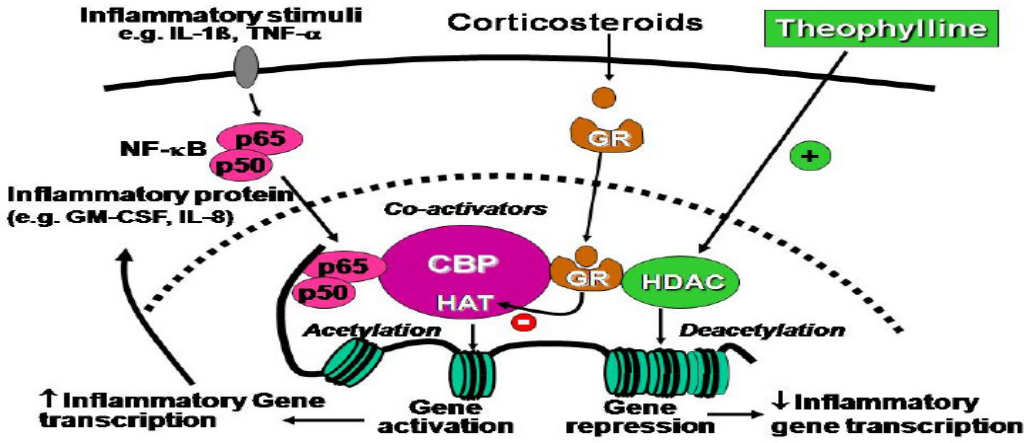


Figure 11: Reversal of steroid resistance - activation of HDAC by theophylline. [(54)]

Theophylline enhances the action of HDAC5 and improve the anti-inflammatory effect of corticosteroids. It also serves to reduce the resistance to steroids in COPD patients. [63] This is encountered at low blood levels and during oxidative stress and stress due to nitrogen and its metabolites. In bronchial asthma theophylline decreases the formation of peroxy nitrite and increases the function of HDAC2. [64]

IMMUNOMODULATORY EFFECT:

Theophylline improves the function of CD8+ T-lymphocytes and decreases the chronic inflammation of the airways .It also reduces IL-4 and IL-5 levels in asthmatics. [65]

EXTRA PULMONARY EFFECTS OF METHYLXANTHINES:

Aminophylline enhances the contraction of diaphragm, thus reducing diaphragmatic fatigue. [66]

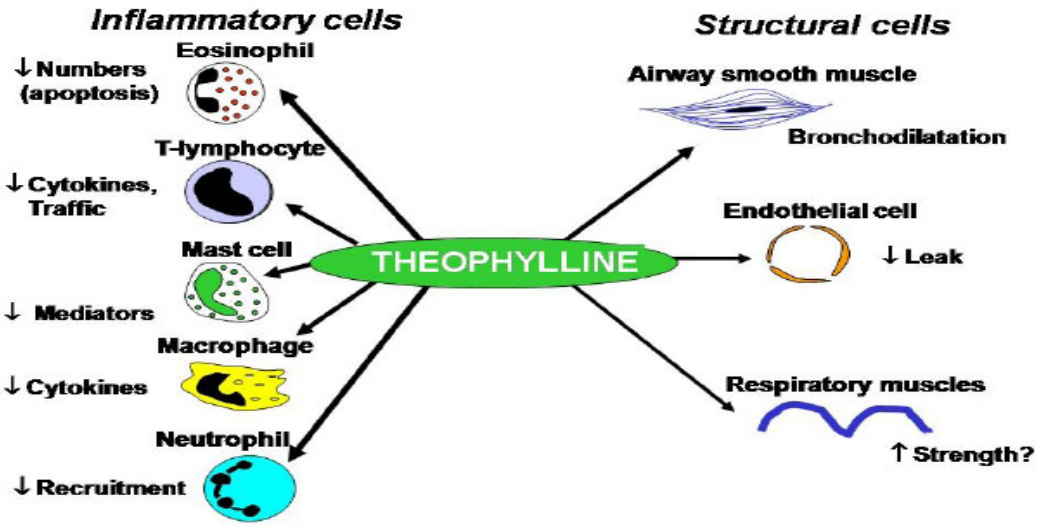


Figure 12: Cellular Effects Of Theophylline[54]

CELLULAR EFFECT:

At cellular level theophylline has multiple actions which pave way in the improvement of bronchial asthma.

PHARMACODYNAMICS OF METHYLXANTHINES:

The effects of methylxanthine are exerted in various organ systems of our body like CNS, kidney, cardiac, skeletal muscles and smooth muscles. Various methylxanthines prefer different tissues for their action .Theophylline has preference for smooth muscles while caffeine acts on CNS.

EFFECTS ON CENTRAL NERVOUS SYSTEM:

These drugs cause cortical stimulation and improve the alertness while decreasing fatigue. They cause nervousness and tremor in few individuals. Higher doses lead to stimulation of medulla, convulsion and death.[67]

CARDIOVASCULAR EFFECTS:

Methylxanthines block the presynaptic adenosine receptors enhancing the concentration of catecholamine in synaptic cleft. This results in positive chronotropic as well as ionotropic effects on heart. Methylxanthine renders the blood less viscous leading to increased blood flow which helps in treating intermittent claudication .Pentoxifylline is used for this purpose.[67]

EFFECTS ON GI TRACT:

Methylxanthine promotes the secretion of gastric acid and other digestive juices.

EFFECTS ON KIDNEY:

Methyxanthine cause mild diuresis as a result of enhanced glomerular filtration as well as decreased tubular reabsorption. But this is a meagre response which could not be utilized therapeutically. [67]

EFFECTS ON SMOOTH MUSCLE:

This relaxation effect is utilised for management of bronchial asthma. No tolerance is encountered for this action.

EFFECTS ON SKELETAL MUSCLE:

Methylxanthine enhance the magnitude of skeletal muscle contraction. It improves the function of diaphragm and leads to better response to hypoxia and decrease dyspnea.

CLINICAL USES

1. ACUTE SEVERE ASTHMA:

Aminophylline was used earlier as an intravenous agent for acute management of severe asthma. Due to its enhanced spectrum of adverse effects, nebulised beta2 agonists are now used in this situation. Aminophylline use is now restricted to non responding individuals.[68]

2. CHRONIC ASTHMA:

In patients who are already on inhaled steroids for asthma control, theophylline demonstrates better level of control than beta2 agonists.[69]

As sustained release formulations, methylxanthines are useful in the management of nocturnal asthma. They provide overnight control symptoms.[70]

3. ADD ON THERAPY:

Studies suggest that including low dose theophylline as add on therapy for patients not responding to inhaled steroids provide better relief than doubling the inhaled steroid dose.[71, 72]

4. COPD:

Theophylline provides increased exercise tolerance, reduces air trapping, stress due to nitrogen in COPD patients.[73]

ADVERSE EFFECTS:

Increased incidence of adverse events limit the use of theophylline. The adverse effects mediated by adenosine receptor inhibition like central nervous system stimulation, gastric acid production, diuretic effect, cardiovascular effects like arrhythmias may be minimised by the use of drugs that inhibit phosphodiesterase or doxofylline.[75]

The unwanted effects mediated through PDE inhibition are nausea, vomiting, palpitations, arrhythmias, headaches [76].

The adverse effects of theophylline correlates with its serum level. It occurs most commonly at the concentrations more than 20mg/l .Few individuals encounter these reactions at lower concentrations itself. Apart from the above

effects, very high concentration may lead to convulsions & cardiac arrhythmias.[6]

CLEARANCE OF METHYLXANTHINES:

The following situations increase the clearance of methylxanthines:

1. Enzyme induction ($CYP1A_2$) by other drugs used simultaneously like rifampicin, barbiturates, ethanol and others.
2. Smoking induces the enzyme $CYP1A_2$ causing increased clearance.
3. A diet rich in protein and low in carbohydrates.
4. Barbecued meat.

The conditions which decrease the clearance of methylxanthine and increase the serum concentration are:

1. Inhibition of cytochrome P450 isoenzyme by other drugs like cimetidine, erythromycin, ciprofloxacin, allopurinol, zileuton, zafirlukast.
2. Congestive cardiac failure
3. Hepatic disease
4. Pneumonia
5. Viral infection
6. Carbohydrate rich diet
7. Geriatric population

DOXOFYLLINE

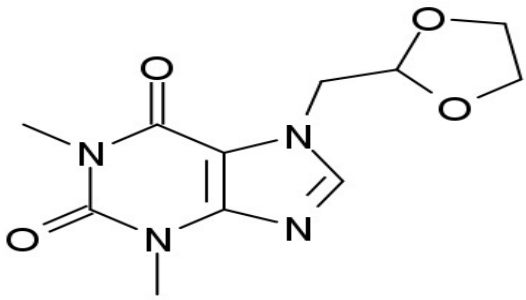


Figure 13: Structure Of Doxofylline

7(1,3 dioxolone-2methyl)theophylline is doxofylline. It differs from theophylline by the presence of dioxolane group in position 7.

PHARMACOKINETICS:

Oral bioavailability is 62.6% peak serum concentration is attained, at about 1.19hr.It takes 6hrs to reach the steady state .AUC of doxofylline is 69.5microgram/ml .It is 48% protein bound with distribution half-life of 0.19hr.Volume of distribution is 1 l/kg.

About 90% of doxofylline is metabolized in liver into inactive metabolite hydroxyethyl theophylline. It is excreted by kidney. Its elimination half-life is 7-10 hours. Dose-400mg o.d / b.d oral.

DERIPHYLLINE

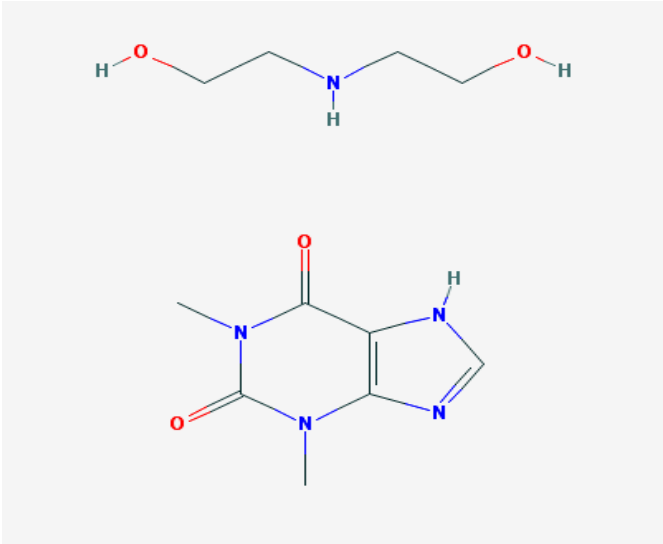


Figure 14: Structure Of Deriphylline

PHARMACOKINETICS:

Theophylline is rapidly and completely absorbed when given orally. Maximal plasma concentration is attained within 2hrs. Food slows down the rate of its absorption. Rate of absorption is decreased by sleep and recumbent position.

Theophylline is uniformly distributed throughout the body, crosses the placenta and secreted in breast milk. Metabolism takes place in liver.15% of drug is excreted in urine. Average half-life of theophylline is about 20-36hrs.

The elimination kinetics of theophylline varies according to its plasma concentration. It follows first order kinetics within the therapeutic range while it changes to the zero order kinetics at higher concentration.[6]

CLINICAL TRIALS ON METHYL XANTHINES

The study done by Goldstein M F, et al. is a double blind randomized place controlled multicentric clinical trial. This study states that the use of doxofylline resulted in a reduction frequency of asthmatic attacks and also significantly lowered the use of salbutamol in asthmatics for symptomatic relief. It also showed enhanced bronchodilatation which is indicated by elevated mean forced vital capacity and peak expiratory flow rate. Adverse reactions are encountered more in the theophylline group.[77]

In this study Cogo R, et al. proposed that there is less inflammatory change and modification in cell proliferation by the use of doxofylline in chronic obstructive bronchitis patients. He found out a marked decrease in bronchial inflammation and infiltration of neutrophils in the bronchoscopy specimens of patients who improved clinically.[78]

Bagnato GF evaluated the tolerability of doxofylline as maintenance therapy. This study throws light on the safety and better side effect profile of doxofylline. [79]

Lazzaronim, et al. conducted a study on duodenal ulcer patient comparing the effects of doxofylline and aminophylline in inducing gastro esophageal reflux. It revealed that less lower esophageal sphincter pressure and change in gastric motility in the patients on doxofylline therapy. He concluded that doxofylline is safer in asthmatic patients who suffer with peptic ulcer disease.[80]

In his study on the effect of doxofylline and theophylline in sleep, Sacco et al. declared that theophylline caused insomnia, increased awakening at night, and less Rapid Eye Movement Sleep when compared with doxofylline.[82]

PERSPECTIVE OF METHYL XANTHINES

Due to the widespread use of ICS, inhaled β_2 agonists, the role of Methylxanthines in asthma is decreasing. But sustained release Theophylline has a prominent place in developing countries as an affordable antiasthmatic drug. Theophylline`s effect not only ends with bronchodilatation but also has other significant effects in asthma patients even at lower serum concentrations.[6]

Combined use of ICS and Theophylline has better effect in severe asthmatics and COPD patients. It is evident that we can add Theophylline instead of doubling the dose of ICS, it can reverse steroid resistance by acting on $HDAC_2$ and helps in COPD patients. Hence Theophylline`s role in asthmatics is essential in developing countries like India. [6, 83]

NOVEL THERAPY FOR BRONCHIAL ASTHMA

SMART STRATEGY:

This is the usage of Single inhaler maintenance and Reliever Therapy. A combination of Budesonide and Formoterol is used as controller and preventer medication in bronchial asthma patients.[84]

INFLAMMATORY MEDIATOR ANTAGONISTS:

As asthma involves a cascade of mediators and various receptors, antagonists of single receptor or mediator will not be effective in bronchial asthma treatment. [6,85]

CRTH$_2$ ANTAGONIST:

These are new class of drugs acting on DP$_2$ receptors of prostaglandin. Crth$_2$ is the chemotactic factor for TH$_2$ cells. These drugs are in trial for usage in bronchial asthma and other allergic disorders.[86]

ENDOTHELIN ANTAGONISTS:

These drugs are used for the treatment of pulmonary hypertension and they may be helpful in treating the structural changes occurring in asthma and COPD.[6]

ANTIOXIDANTS:

Antioxidants like Vit. C, Vit E, N-acetyl cysteine reduce the oxidative stress which participates in steroid resistance in asthma and COPD.[87]

CYTOKINE MODIFIERS:

Reslizumab is a monoclonal antibody against IL-5. Blocking IL-5 interferes with eosinophilic survival and priming. This resulted in reduced sputum eosinophils and some improvement in symptoms.

Pitrakinra blocks the IL-4 receptor reducing the late response to allergic stimuli in bronchial asthma patients.[89]

Lebrikizumab, a monoclonal anti body against IL-13, produces an increase in FEV, in some asthmatics.[90`]

CHEMOKINE RECEPTOR ANTAGONISTS:

Mogamulizumab, antibody to CCR4 causes decreased TH2 production which is tried in asthmatics as well as T Cell leukemia / Lymphoma patients.[92] Navarixin, CXCRI / CXCR2 antagonist blocks neutrophils in sputum which is on trial for asthma.[93]

NEW ANTI- INFLAMMATORY DRUGS:

Phosphodiesterase 4 inhibitors, Nfk- B inhibitors, MAP – Kinase inhibitors, mast cell inhibitors, Mucoregulators, Mucolytics PPAR γ agonists are all tried in asthma. [94,95, 96 ,97,98,99,100,101]

NOVEL CLASSES OF BRONCHODILATORS:

Ultra LABA like indacaterol, carmoterol, vilanterol, olodaterol which are used along with inhaled steroids, are used as once daily dosage in asthmatics.[102]

NONSTEROIDAL SELECTIVE GLUCOCORTICOID RECEPTOR ACTIVATORS:

Nonsteroidal selective glucocorticoid receptor activators (mapracorat) also known as disassociated corticosteroids have differential action. The transactivation in disassociated from transrepression leading to better therapeutic effects and lesser side effects. [104]

NON ANTIBIOTIC MACROLIDES:

These are new class of drug which do not have antibiotic effect but have anti-inflammatory effect by inhibiting NE Kb. These drugs also found to reverse the steroid resistance caused by oxidative stress. [105]

Materials and Methods

MATERIALS AND METHODS

SOURCE OF DATA:

Patients diagnosed to have mild to moderate persistent bronchial asthma, attending the Thoracic medicine out- patient department of Chengalpattu Medical College Hospital.

COLLABORATING DEPARTMENTS:

Department of Pharmacology, Pathology, Medicine, Radiology Thoracic Medicine, Chengalpattu Medical College.

ETHICAL CLEARANCE:

Obtained on 11.06.2014

METHODS OF DATA COLLECTION:

Study Design : Randomized prospective, open labeled comparative study

Study Period : 1 year (Jul2014-Jun2015)

Sample Design: Randomised sample

Sample Size : 186

Inclusion Criteria:

1. All adult patients (> 18 years of age) diagnosed with mild to moderate persistent bronchial asthma (may use concomitant medications as and when needed according to the severity)
2. Willing for investigations

3. Agree to give informed written consent
4. Willing for follow up visits

Exclusion Criteria:

1. Major respiratory illness other than asthma like chronic obstructive pulmonary disease or other relevant lung disease causing impairment in lung function.
2. Patients with co-morbid conditions – Ischemic heart disease, congestive cardiac failure, renal and hepatic dysfunction, neurological endocrinal haematological and other abnormalities..
3. Pregnant and lactating women.
4. History of known allergy/intolerance/hypersensitivity to study drugs.
5. Patients on regular treatment with drugs that interact with methylxanthines
6. Patients < 18 years of age
7. Patients who do not give consent for the study.
8. Discontinuation Criteria:
9. Patients were permitted to discontinue from the study if they decided to do so.

ASSESMENT TOOLS

- INFORMED CONSENT

Informed consent form which clearly sates the details of the study and has written consent in both English and regional language was used. The study was explained to the participants in their own language and written informed consent was got.

- PREVIOUS HISTORY AND PHYSICAL EXAMINATION**:**

A detailed history along with thorough physical examination was done and the same is recorded in the case sheet.

- ASSESSING THE COST OF TREATMENT:

Information required for calculating the cost of treatment like wages, accompanying person details, distance from the health facility and other relevant information are collected and recorded.

- USE OF PARAMETERS:

Parameters like weight and height are taken. BMI is calculated by Quetelet`s index,

$$\text{BMI} = \frac{\text{Weight in Kilograms}}{\text{Height in M}^2}$$

- VITALS:

Pulse (beats/ min), Blood pressure (mm Hg)

This is measured using sphygmomanometer while the patient is in supine position.

Respiratory rate - Measured by palpating the movement of chest wall of the patients.

- ASSESSMENT OF EFFICACY:

(i) Spirometry:

It is a measure of airflow and lung volumes during a forced expiratory from full inspiration. It is fundamental to the diagnosis and assessment of airway disease. Parameters used as tools and FVC, FEV, FEV1/FVC and PEFR. [42]

(ii) Asthma Control Test:

This score helps to differentiate the levels of symptom control and used to evaluate the progress of the patient. The test has 5 questions, 4 of which pertain to symptoms and one is the patient`s self assessment of his level of asthma control. The maximum score is 25 and each question carries 5 points. A score of 20-25 is taken as patient with well controlled asthma, 16-20 not well controlled, 5- 15 are poorly controlled.[42]

(iii) Subjective rating of asthma control:

This scale consists scores in percentage. 0% indicates no control and 100% means very well controlled asthma. The subjective rating is done by the patient considering his/her symptom control since last visit.

- ASSESSMENT OF SAFETY:

Safety is assessed by adverse drug reactions which are reported by the patients, or enquired by the investigators, or from the observations of clinical examinations and laboratory reports.

- ASSESSMENT OF COST EFFECTIVENESS:

Cost: By calculating the direct and indirect costs[119].

Health Outcome: By the level of symptom – relief and free from side effects[119].

- PATIENT`S REVIEW SCHEDULE:

(i) First Visit: The following were done in day I.

- The entire study is explained to the patients including the purpose, procedure health benefits and written informed consent was obtained from each.
- Patients were recruited according to the protocol.
- Patient`s living place, means of transport medical history, concomitant medical history and other relevant information necessary for assessing cost were taken.
- A detailed physical examination was done.

- Baseline investigations for asthma and lab parameters were performed for all patients recruited for the study.
- Treatment given according to the group the patients belong.
- All were advised to come for regular follow up and assessment in 4 weekly interval was carried out for a period of 12 weeks.

➢ Follow up visit:

- Done at 4^{th}, 8^{th} and 12^{th} weeks.
- The patients were assessed for symptom control and clinical improvement using spirometry, asthma control test, and subjective rating of asthma control for subsequent period of visits.
- Information about adverse reactions - voluntarily reported, observed and enquired were all collected.
- Health education regarding asthma control was given to the patients in order to sustain their compliance.

➢ At their visit on the 12^{th} week, all laboratory parameters assessed at the baseline were again repeated.

➢ ANALYSIS:

The data collected were analyzed using Student t test (two tailed, independent) to find the significance of study parameters on continuous scale between two groups (Inter group analysis) on metric parameters. Chi-square/ Fisher Exact test was used to find the significance of study parameters on categorical scale between two or more groups.

Results

RESULTS

186 patients were initially recruited for the study. Out of this, 26 patients were excluded from the analysis due to the following reasons: 21 patients were lost to follow up and 6 patients discontinued from the study 160 patients were analyzed for the study.

GENDER AND AGE DISTRIBUTION

Among the 160 patients participated in the study, 38.8% in doxofylline group and 34% in deriphylline group were females and the rest were males.

Sex	Doxofylline group	Deriphylline group	Total	Chisq	p value
F	31	34	65	0.233	0.6
M	49	46	95		
Total	80	80	160		

Table 3: Gender distribution

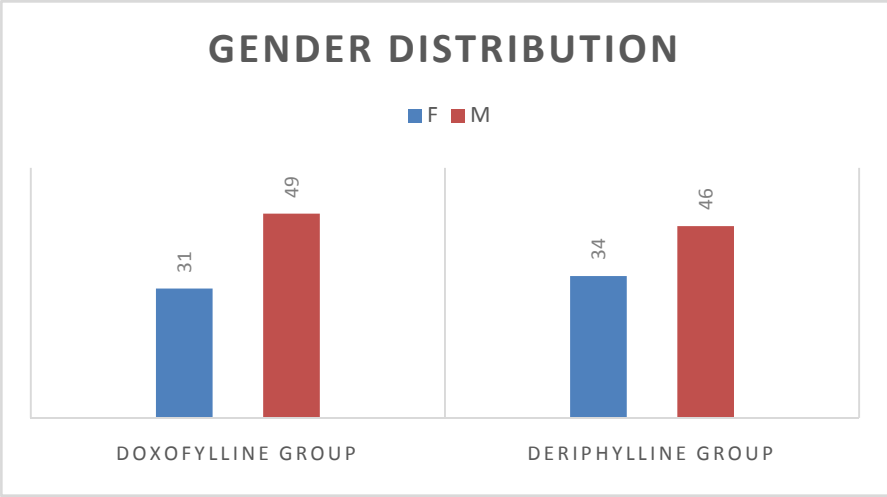


Figure 15: Gender Distribution

	Doxofylline group	Deriphylline group
Age	45.31±7.5	44.08±9.6
BMI	21.386±3.04	21.688±3.3
FAMILY HISTORY		
NIL	60	47
ALLERGY	1	10
BRONCHIAL ASTHMA	19	23
DURATION	6.97±3.57	7.46± 4.63
AGGRAVATING FACTOR		
NIL	20	18
%	25%	22.50%
Dust	36	30
%	60%	48.39%
Air pollution	8	11
%	13%	17.74%
cold weather	18	21
%	30.00%	33.87%

Table 4: Comparison of Age, BMI, Family history, Aggravating Factor

AGE:

Mean age of the patients in doxofylline group was 45.31±7.5 and those in deriphylline group was 44.08±9.6.

BODY MASS INDEX:

The mean BMI of the patients participated in doxofylline group was 21.30 while that of deriphylline group was 21.69

DURATION OF ILLNESS:

The patients recruited for doxofylline group had bronchial asthma for the mean duration of 6.97±3.57 years and the deriphylline group patients had the illness for a mean duration of 7.46±4.63 years.

AGGRAVATING FACTORS:

75% of the patients on doxofylline and 77.5% of patients on deriphylline had one or the other aggravating factors. In majority of patients, environmental dust is a major cause in aggravating asthma (60% in doxofylline group and 48.39% in deriphylline group). The contribution of other factors are as shown in the table.

FAMILY HISTORY:

No family history was present in 60 patients of doxofylline group and 10 patients in deriphylline group. History of bronchial asthma was present in 19 of doxofylline and 23 patients of deriphylline group. 10 persons in deriphylline group had family history of allergy.

ESTIMATION AND COMPARISON OF EFFICACY:

Asthma Control Test questionnaire score

	Doxofylline	Deriphylline	P value
Baseline	16.05±0.87	17.21±1.41	0.209
I visit	17.88±1.24	18.14±1.38	0.00
II visit	20.19±1.33	19.5±1.4	0.002
III visit	24.42±1.12	20.69±1.08	0.003

Table 5: Asthma Control Test questionnaire score

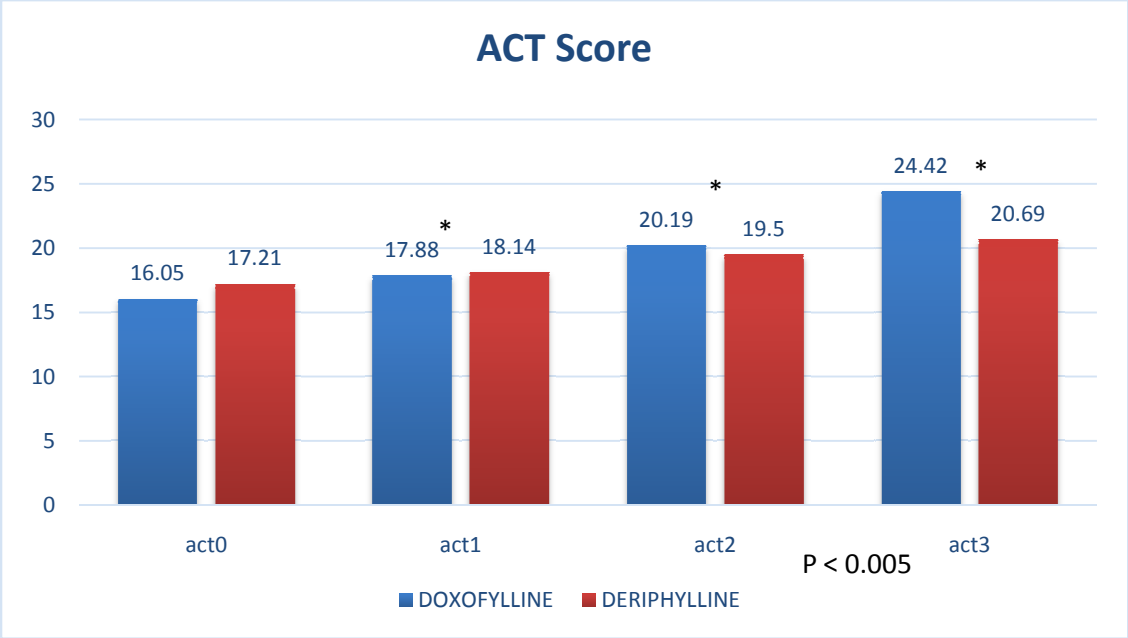


Figure 16: Asthma Control Test questionnaire score

	Baseline	III visit	P value
Doxofylline	16.05±0.87	24.42±1.12	0.002
Deriphylline	17.21±1.41	20.69±1.08	0.001

Table 6: ACT Score - Improvement from baseline

The level of control of the disease as assessed by asthma control test questionnaire revealed that there was statistically significant improvement in both groups compared with baseline and a significant difference between the doxofylline group and the deriphylline group throughout the study.

Subjective rating of asthma control

	Doxofylline	Deriphylline	P value
Baseline	48.62±10.6	57.56±7.83	0.789
I visit	62.32±7.29	62±8.0	0.00
II visit	74.56±8.16	68.44±6.82	0.00
III visit	84.94±4.87	74.06±6.01	0.00

Table 7: Subjective rating of asthma control

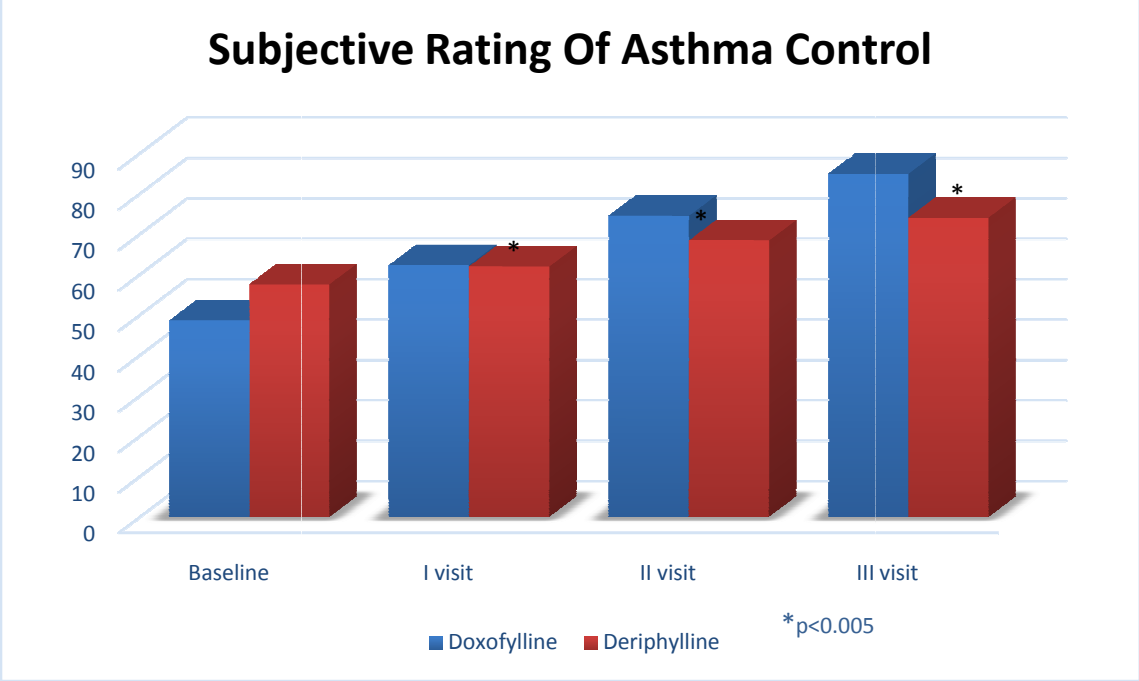


Figure 17 : Subjective Rating Of Asthma Control

	Baseline	III visit	P value
Doxofylline	48.62±10.6	84.94±4.87	0.0001
Deriphylline	57.56±7.83	74.06±6.01	0.0001

Table 8: Subjective Rating Of Asthma Control-Improvement From Baseline

The results of subjective rating of asthma control showed significant increase in both groups compared with the baseline and subsequent visits. Significant improvement is encountered in the doxofylline group compared with the deriphylline group in all visits.

Comparison of forced vital capacity of the two groups of patients

	Doxofylline	Deriphylline	P value
Baseline	60.53± 3.72	61.23± 8.67	0.51
I visit	68.32± 2.62	81.9± 7.97	0.13
II visit	76.58± 2.57	77.4± 5.27	0.21
III visit	81.48±2.06	89.95± 4.87	0.39

Table 9: Comparison Of Forced Vital Capacity

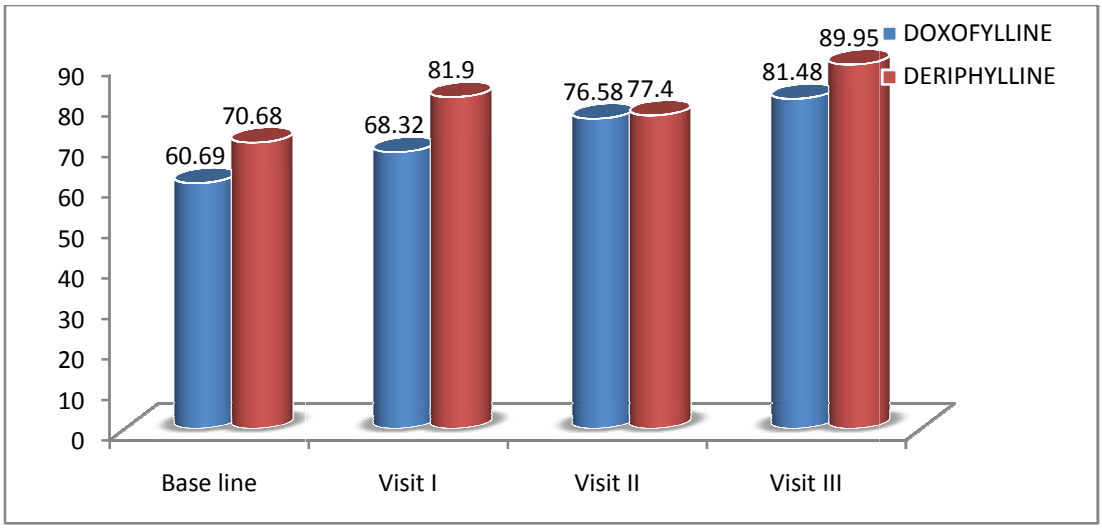


Figure 18: Comparison Of Forced Vital Capacity

	Baseline	III visit	P value
Doxofylline	60.53±3.72	81.84±2.06	0.0001
Deriphylline	61.23±8.64	89.95±4.87	0.0001

Table 10: Comparison Of Forced Vital Capacity- Improvement From baseline

The results of lung function tests using spirometric parameters displayed a significant increase in the percentage predicted forced vital capacity in both the study groups compared to the baseline in subsequent visits. There was no statistically significant difference between two groups indicating both the drugs are equally efficacious.

Comparison of percentage predicted from forced expiratory volume at the end of 1 second

	Doxofylline	Deriphylline	P value
Baseline	59.96±1.68	59.76±4.68	0.72
I visit	67.02±2.04	66.5±4.16	0.314
II visit	73.03±3.55	72.98±3.2	0.93
III visit	77.51±6.57	77.42±2.24	0.94

Table 11: Forced Expiratory Volume At The End Of 1 Second

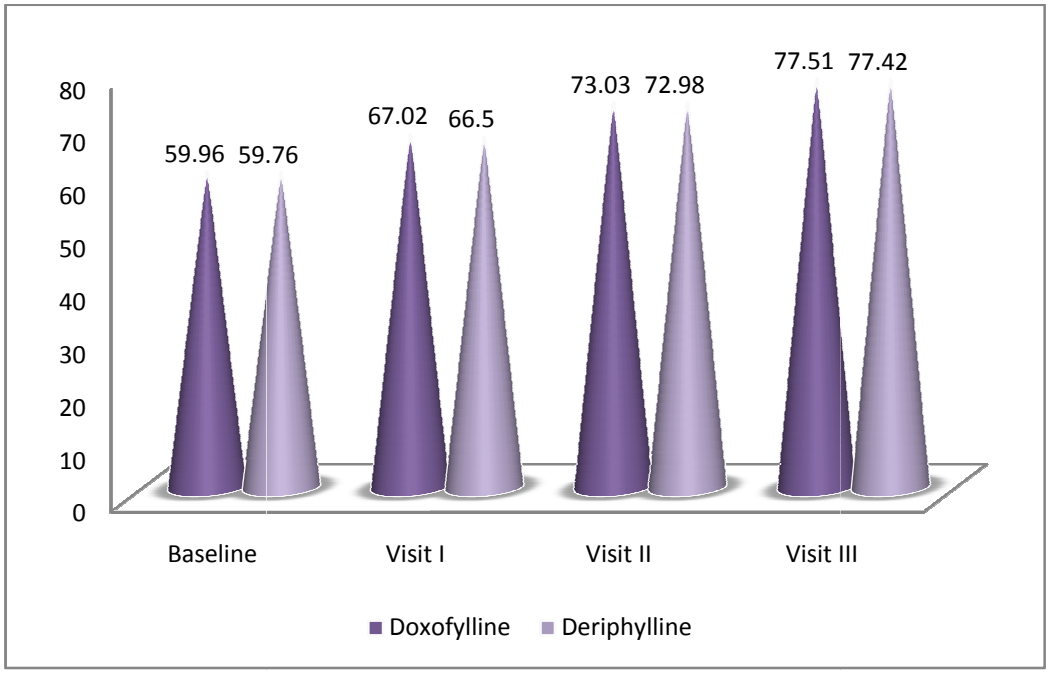


Figure 19: Forced Expiratory Volume At The End Of 1 Second

	Baseline	III visit	P value
Doxofylline	59.96±1.68	77.51±6.57	0.0001
Deriphylline	59.76±4.68	77.42±2.24	0.0001

Table 12: Forced Expiratory Volume At The End Of 1 Second-Improvement From Baseline

Percentage predicted about forced expiratory volume at1 second is a spirometric parameter which showed no significant difference between both groups of study while there was significant improvement in both groups from the baseline to the III visit.

Comparison of percentage of predicted peak expiratory flow rate in both the study group:

	Doxofylline	Deriphylline	P value
Baseline	60.62±1.99	68.38±5.68	0.225
I visit	67.33±3.38	67.81±4.36	0.973
II visit	71.89±3.66	71.84±3.56	0.92
III visit	76.83±4.66	76.84±2.78	0.99

Table 13: Peak Expiratory Flow Rate

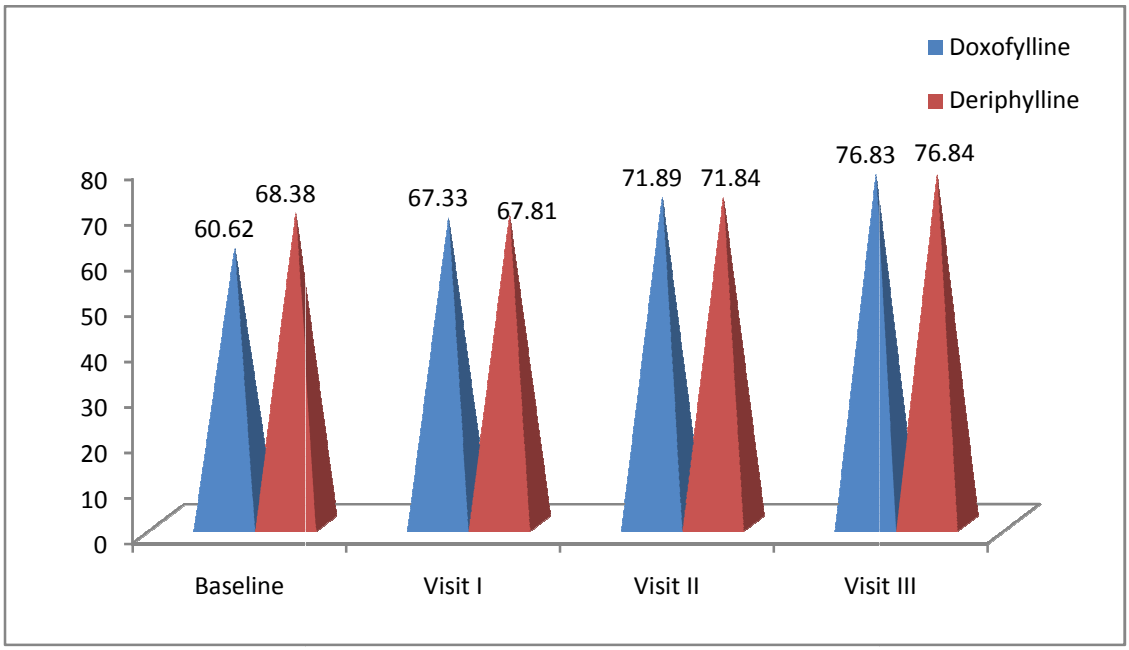


Figure 20: Peak Expiratory Flow Rate

	Baseline	III visit	P value
Doxofylline	60.62±1.99	76.83±4.66	0.0001
Deriphylline	68.38±5.68	76.84±2.78	0.0001

Table 14: Peak Expiratory Flow Rate- Improvement From Baseline

The results of peak expiratory flow rate suggests that there exists significant improvement in Doxofylline as well as deriphylline group participants compared to the baseline. There is no significant difference seen in the efficacy between the two study groups statistically which implies the two groups are equally efficacious.

Comparison of FEV_1/FVC of both the study group patients:

	Doxofylline	Deriphylline	P value
Baseline	62.91±1.93	62.58±3.8	0.48
I visit	66.56±3.47	66.51±3.63	0.93
II visit	73.6±3.77	73.58±3.21	0.96
III visit	77.22±4.63	77.25±2.74	0.96

Table 15: Comparison of FEV_1/FVC

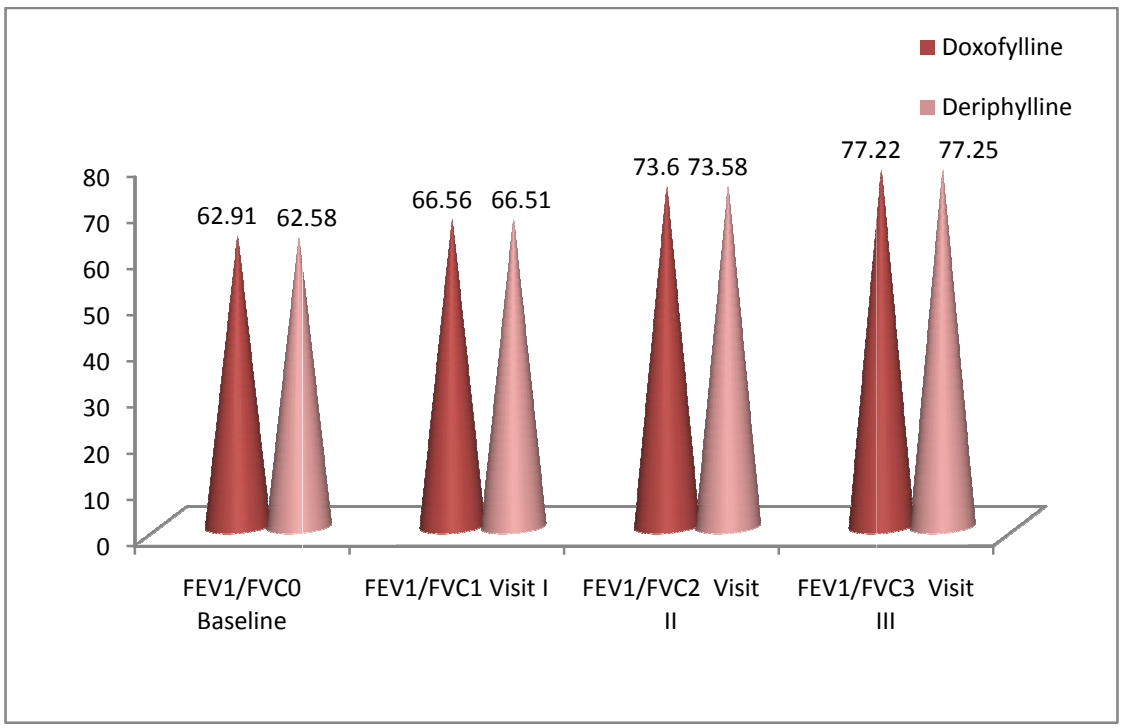


Figure 21: Comparison of FEV_1/FVC

	Baseline	III visit	P value
Doxofylline	62.91±1.93	77.22±4.63	0.0001
Deriphylline	62.58±3.8	77.25±2.74	0.0001

Table 16: Comparison of FEV_1/FVC - Improvement From Baseline

Analysis of FEV_1/FVC of the study population showed that there was significant improvement in both the groups when compared with the base line. At the same time there was no significant difference between both the groups in terms of efficacy.

ESTIMATION AND COMPARISON OF SAFETY PROFILE

Adverse reactions encountered among the participants

10% of the Doxofylline group participants had adverse reactions while 22% of Deriphylline group had the same. The incidence of adverse reactions were significantly high in deriphylline group with a P value of < 0.001.

	DOXOFYLLINE GROUP		DERIPHYLLINE GROUP		P value
ADR	No. of Patients	Percentage	No. of Patients	Percentage	
NIL	73	91.2	18	22.5	<0.001
Epi gastric pain	2	2.5	7	8.8	
Giddiness	2	2.4	4	5	
Nausea	2	2.5	14	17.5	
Palpitation	1	1.2	8	10	
Headache	-	-	10	12.5	
Insomnia	-	-	4	5	
Tachycardia	-	-	2	2.5	
Tremor	-	-	10	12.5	
Vomiting	-	-	3	3.8	
Total	80	100	80	100	

Table 17: Adverse reactions encountered among the participants

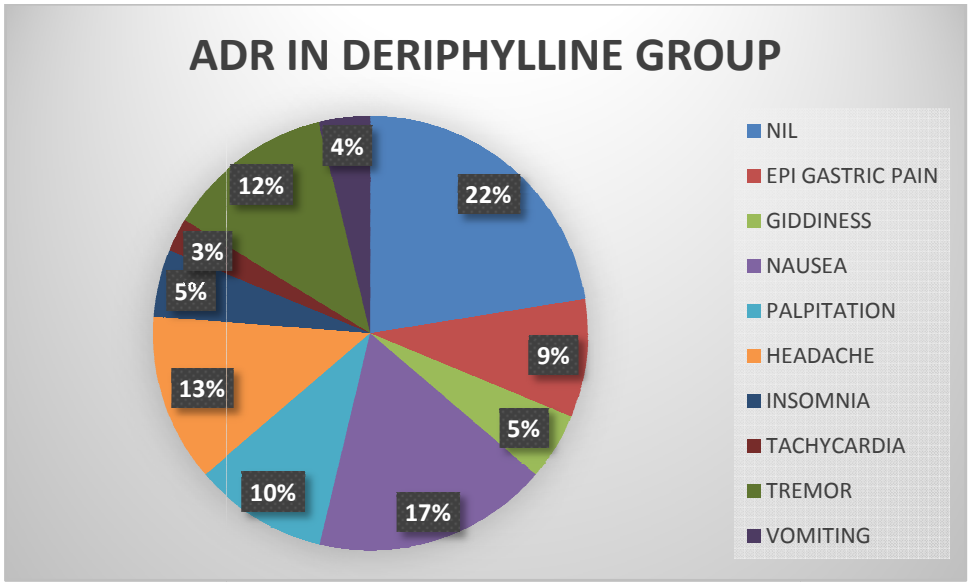


Figure 22: Deriphylline Group - Adverse Reactions Among The Participants

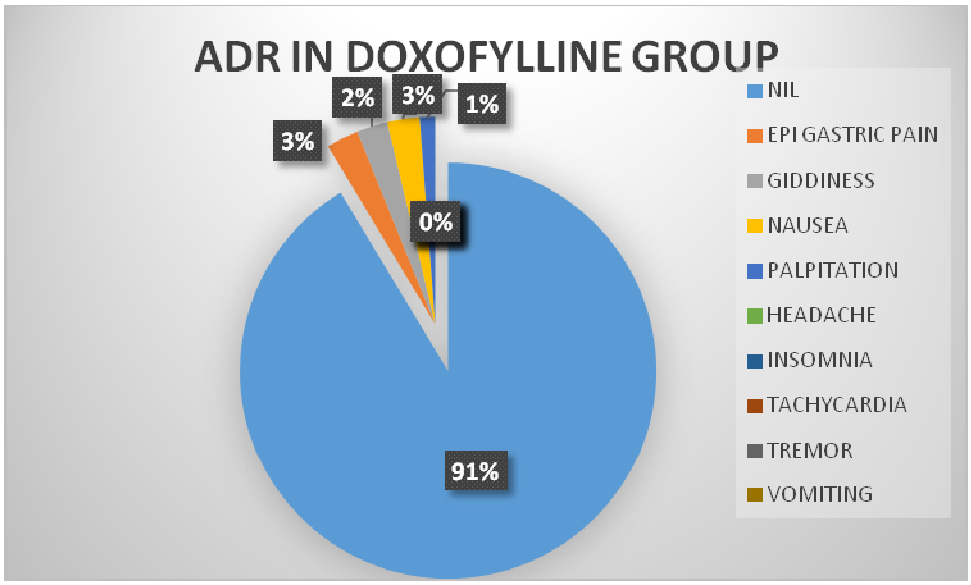


Figure 23: Doxofylline Group - Adverse Reactions Among The Participants

Adverse reactions like vomiting, tremor, tachycardia, insomnia, head ache etc. are not seen in doxofylline group. Also epigastric pain, giddiness, nausea and palpitation are less in doxofylline group compared with deriphylline group.

The management of adverse reactions is done by appropriate therapy; with H_2 receptor antagonists, Proton pump inhibitors, antihistaminics etc.

Comparison of laboratory investigations:

The laboratory investigations done at the baseline and at the end of the study period showed no significant difference in the parameters tested.

ECG:

The baseline ECG in both groups were within normal limits. During the course of study, 3 participants in deriphylline group had sinus tachycardia in the ECG which was managed conservatively. The doxofylline group patients had no such abnormalities in the ECG.

CHEST X-RAY:

At the start of study, chest x-ray of 3 patients in deriphylline group and 2 patients in doxofylline group had changes suggestive to hyperventilation, which persisted till the end of the study. The CXR of the other patients were within normal limits at the beginning and end of the study.

ESTIMATION OF COST:

The estimation of treatment cost was done by summing up the direct and indirect costs. The direct cost included the cost of treatment of disease, adverse events and investigations. The indirect cost accounted for travelling expenses, food expenses and loss of wages of the patient and the accompanying person.

COMPARISON OF TOTAL COST:

	Doxofylline	Deriphylline	P value
Mean cost for 3 months (in rupees)	503.99±131.4	205.09±160.47	0.00

Table 18: Comparison Of Total Cost

In this study, the mean cost for treating a patients with doxofylline was significantly more than that of deriphylline.

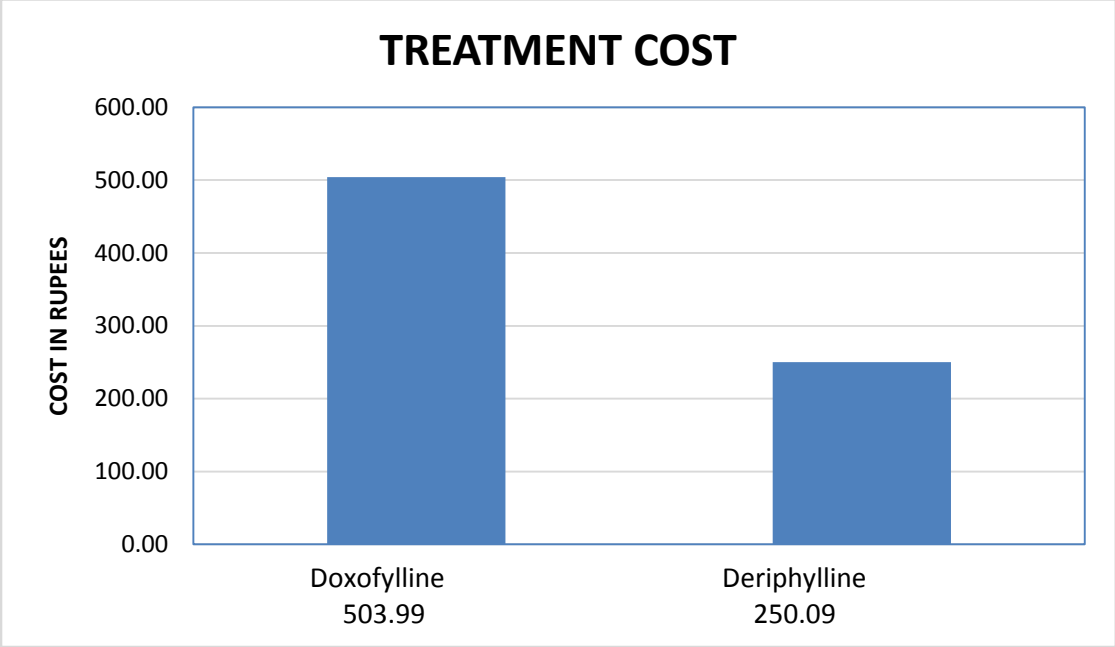


Figure 24: Treatment Cost

One year mean expense of treating a patient with doxofylline was Rs.2016 ±524.59 while that of deriphylline was Rs.1000.30 ± 641.91. The mean cost for treating a patients with doxofylline was significantly higher (P=0.0001).

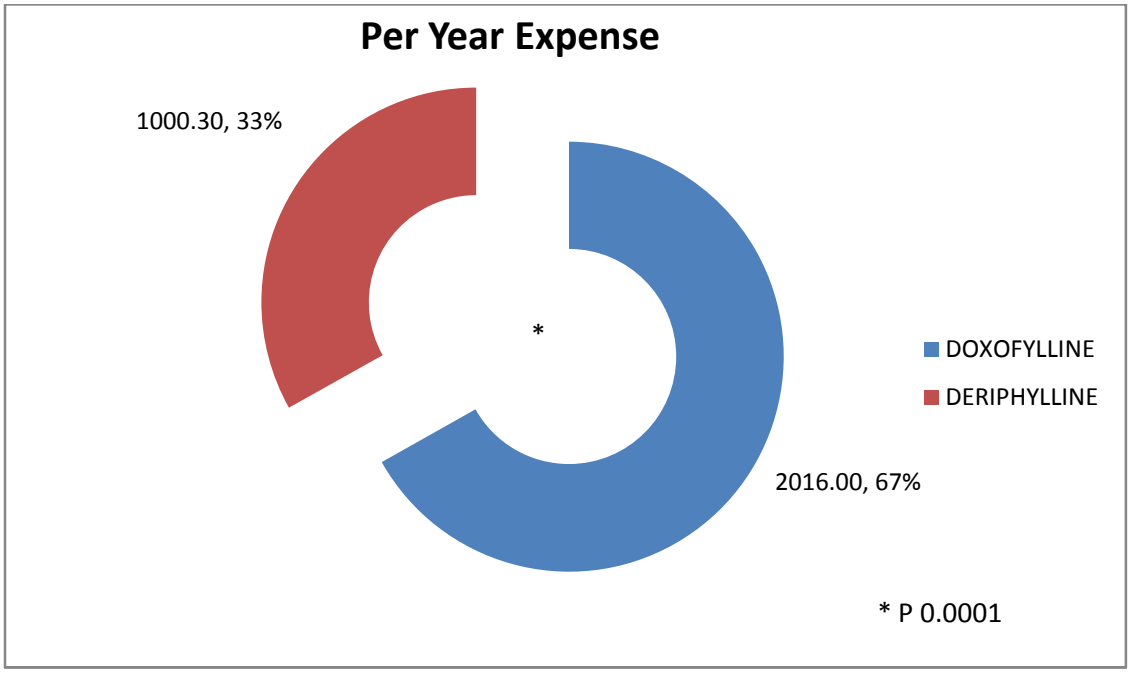


Figure 25: Expense For 1 Year

ESTIMATION OF EFFECTIVENESS:

In this study, the effectiveness is estimated as significant asthma control.

COMPARISON OF EFFECTIVENESS:

Both the study drugs provide significant improvement in bronchial asthma patients. There was no statistically significant difference between both study group in terms of effectiveness. The patients treated with doxofylline experienced less adverse events while the patients in the deriphylline group witnessed statistically significant increase in the adverse reactions.

Discussion

DISCUSSION

Bronchial asthma is a chronic airway inflammatory disease with a worldwide prevalence of 1-18%. Variety of triggers are attributed to its causation. The disease brings about variable airflow limitation which results in wheeze, shortness of breath, chest tightness and cough.

The pharmacotherapy consists of relievers, controllers and add-on therapies. Methylxanthines are used as reliever medication and can be used conveniently in oral route. In developing countries like India, oral methylxanthines are the commonly used drug in the population level. To obtain data about methylxanthines with bronchodilatory properties, less adverse reactions and at a lower cost, this study is conducted.

This prospective observational study of efficacy, safety and cost effectiveness of doxofylline and deriphylline in mild to moderate persistent bronchial asthma patients, involved 160 patients. The diagnosis was done in proportion to the guidelines of global strategy for diagnosis and prevention of bronchial asthma, update -2014.

The enrolment was done after obtaining written informed consent. It was conducted in the Thoracic medicine department of Chengalpattu medical college for a duration of 12 weeks over a period of 1 year. The participants were evaluated and analyzed for epidemiological profile, disease activity, efficacy, safety and cost effectiveness parameters.

The mean age of the participants in doxofylline group was 45 years and that of deriphylline group was 44 years. Doxofylline group had bronchial asthma for the mean duration of 6.97±3.57 years and the deriphylline group patients had the illness for a mean duration of 7.46±4.63 years.

Aggravating factors are present in 75% of patients under doxofylline and 77.5% of patients under deriphylline treatment. Dust, cold weather and air pollution were attributing factors of illness.

Family history of bronchial asthma was present in 25% of patients in doxofylline group and 28% in deriphylline group. There is a positive association between the presence of asthma in the family and development of airway hyper responsiveness as established by studies done by Blair.s.et al., and young s.et.al,

A mean BMI OF 21.39 is seen in patients with doxofylline therapy and a BMI of 21.69 is seen in patients on deriphylline therapy.

EFFICACY PARAMETERS:

Assessment of Asthma Control Test questionnaire showed statistically significant improvement in all the study participants when compared with the baseline. The study further showed a significant difference between the two groups. The fact that there was better asthma control in doxofylline group than deriphylline group. The finding coincides with the study done by Patel yet al. on bronchial asthma using controller medications as add-on therapy to ICS and LABA. They used montelukast, doxofylline and increased dose of ICS in their

study.[110] ACT can be used in primary care settings to judge the asthma control. This tool can be easily used by trained personnel.[111]

Analysis of subjective rating of asthma control revealed that there was statistically significant improvement from the baseline rating to the end of study rating. The significant improvement in doxofylline group over the deriphylline group indicates that doxofylline had better control over bronchial asthma. This result is consistent with the study conducted by Gold stein MF et. al. They did a double blinded placebo controlled multicentric clinical trial involving 346 patients having bronchial asthma. This study showed that there was significant reduction in the frequency of asthma with doxofylline 400mg as compared to that of theophylline ($P<0.05$)[112]

Spirometry parameters measured in this study demonstrated significant improvement in both the groups comparing the baseline and the end values of the study (P=0.0001). No statistically significant difference established between the two groups. Comparing the baseline parameters to the study end parameters we got 19% and 28 % improvement in FVC, 17% improvement in FEV, 16% and 8% improvement in PEFR and FEV_1/FVC ratio improved by 15. A randomized controlled trial was done by Dolcetti et al. compared doxofylline and placebo. The results of that study indicated a significant improvement in FEV_1 (<20%after 2 hrs.) as compared to the baseline.[112]Another double blinded randomized multicentric trail conducted by Melillo.G et al. showed significant improvement in spirometry parameters with doxofylline and Theophylline.[113]

SAFETY PARAMETERS:

The clinical use of methylxanthines are restricted due to its adverse effect profile. Hence there is a constant search for a newer drug with less incidence of adverse events. In this study, doxofylline had a lower number of adverse events compared with deriphylline. Adverse reactions are encountered in 10% of doxofylline and 22% of deriphylline group. The adverse events like epigastric pain, giddiness, nausea, palpitation are seen only in deriphylline group and not in doxofylline group. Decrease in incidence of adverse reactions in doxofylline group ensures the increase in safety of its utility. In a study done by Bossi.F. et al. doxofylline showed a better tolerability than theophylline.[113, 114.] The suggested reasons for this are its lower affinity towards A, and A_2 adenosine receptors, it does not interfere with calcium influx, and also it does not antagonize calcium channel antagonists. These characters distinguish doxofylline from deriphylline .In therapeutic dose doxofylline is a less cardiac stimulant than deriphylline. It does not increase the cardiac frequency nor is arrhythmogenic.[115]

Deriphylline increases the gastric acid, pepsin secretion and the gastrointestinal motility. As this also plays a role in reducing the pressure in inferior oesophageal sphincter, patients on deriphylline suffer with gastroesophageal reflux disease. Doxofylline has fewer gastrointestinal side effects and tolerated well by the patients with acid peptic disorder.[116]

Deriphylline alters the pattern and quality of sleep leading insomnia and frequent wakening. The study conducted by Sacco et al., the patients on theophylline experienced double the number of arousals than that of subjects without any medications. This reduced quality of sleep does not exist with the use of doxofylline, which again contributing better tolerability of doxofylline than theophylline.[117]

Goldstein and Cherrinsky conducted a study which showed doxofylline of dose 1200mg/day had lower dropout rates due to adverse reactions compared with theophylline group.[77] a study conducted in paediatric population by Bagnato et al. with doxofylline showed 11% adverse effects[118] which matches with the observation of our study showing 10% adverse reactions in doxofylline group.

COST EFFECTIVENESS

The mean total cost of treating a patient with doxofylline was Rs.504 and for deriphylline was Rs.250 in the study period. The higher expense of treating with doxofylline was due to its higher cost. Even though we spent extra cost in treating the more number of adverse effects encountered by deriphylline group patients, this expense was surpassed by the cost of doxofylline. In developing countries owing to the higher cost of treatment with doxofylline, we can opt deriphylline which is equally efficacious at the population level. Doxofylline can be reserved for use in selected patients who cannot tolerate or encounter more adverse reactions due to deriphylline.

Conclusion and Summary

CONCLUSION AND SUMMARY

Asthma is a chronic disease with worldwide prevalence affecting all age groups contributing to the health care burden of the society. A lot of novel medications have been introduced and current guidelines suggest the use of anti-inflammatory therapy in all patients with chronic or persistent asthma. Corticosteroids, mast cell stabilizers, leukotriene receptor antagonists and methylxanthines are effective preventive therapy. Methylxanthines have bronchodilator, immunomodulation, mucoregulator, anti-inflammatory, inflammatory cell stabilizing and steroid sparing properties. They can be used as combination therapy with inhaled steroids in the treatment of mild to moderate persistent bronchial asthma.

The present study done at the Thoracic Medicine Department, Chengalpattu Medical College hospital is a prospective open labeled study comparing doxofylline and deriphylline in 160 patients of mild to moderate persistent bronchial asthma .The patients were assessed for epidemiological profile, spectrum of disease, efficacy, safety and cost effectiveness.

This study revealed that the treatment with both doxofylline and deriphylline resulted in significant bronchodilatation compared to the baseline. Regarding efficacy, doxofylline was better than deriphylline in subjective parameters of asthma control test questionnaire and subjective rating of asthma control but had equal efficacy with spirometric parameters.

In terms of safety, doxofylline was significantly safe compared to deriphylline. The frequently observed adverse effects were nausea, insomnia in both study groups. Tachycardia, palpitation, epigastric pain, vomiting were the other untoward effects seen with deriphylline and not noted in doxofylline.

The cost effective analysis revealed that deriphylline was the cheaper and cost effective methylxanthene for the treatment of bronchial asthma in developing countries at population level. Doxofylline even though costlier had better safety profile with less adverse reactions compared to deriphylline on individual based approach.

LIMITATIONS OF THE STUDY

1. Larger sample size would be considered for better results.
2. Plasma drug concentrations and other pharmacokinetic parameters were not done due to the cost.
3. Daily monitoring with peak flow meter was not done due to logistics and cost.
4. Incremental cost effectiveness ratio is not calculated since it was not feasible in the present setup.

SCOPE FOR FURTHER RESEARCH

1. Pharmacokinetic parameters including plasma drug concentrations of various methylxanthines can be assessed for efficacy, safety and tolerability.
2. Pharmacoeconomic analysis can be done on a large sample of population involving multiple centres.

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Annexures

ANNEXURE I

STUDY PROFORMA

DATE:

PATIENT INFORMATION:

NAME: IP/OP No.:

AGE: yrs. Ht

GENDER: Male / Female. Wt:

OCCUPATION: BMI:

ADDRESS:

PHONE NUMBER:

HISTORY:

DURATION OF THE ILLNESS:

COUGH:

BREATHLESSNESS:

CHEST TIGHTNESS:

WHEEZE:

PRECIPITATING/AGGRAVATING FACTORS:

1. DUST IN THE ENVIRONMENT: YES / NO

2. CIGARETTE SMOKE: YES / NO

3. COLD WEATHER: YES / NO

4. AIR POLLUTION: YES / NO

SIGNIFICANT PAST HISTORY:

PERSONAL HISTORY:

HISTORY OF ALLERGY:

FAMILY HISTORY OF BRONCHIAL ASTHMA: YES/ NO

GENERAL PHYSICAL EXAMINATION:

VITALS:

- PULSE RATE:
- BLOOD PRESSURE:
- RESPIRATORY RATE:

SYSTEMIC EXAMINATION:

CVS

RS

P/A

CNS

ASTHMA CONTROL TEST

To complete it, please mark √ in the one box that best describes your answer.

1. In the past 4 weeks, how much of the time did your asthma keep you from getting as much done at work, school or at home?

All of the time	**Most of the time**	**Some of the time**	**A little of the time**	**None of the time**
1 □	2	3	4	5

2. During the past 4 weeks, how often have you had shortness of breath?

More than once a day	**Once a day**	**3 to 6 times a week**	**Once or twice a week**	**Not at all**
1 □	2	3	4	5

3. During the past 4 weeks, how often did your asthma symptoms (wheezing,

coughing, shortness of breath, chest tightness or pain) wake you up at night or earlier than usual in the morning?

4 or more nights a week	**2 to 3 nights a week**	**Once a week**	**Once or twice a week**	**Not at all**
1 □	2	3	4	5

4. During the past 4 weeks, how often have you used your rescue inhaler or nebulizer medication (Salbutamol)?

3 or more times per day	**1 or 2 times per day**	**2 or 3 times per week or less**	**Once a week**	**Not at all**
1 □	2	3	4	5

5. How would you rate your asthma control during the past 4 weeks?

Not at all Controlled	**Poorly Controlled**	**Somewhat Controlled**	**Well Controlled**	**Completely Controlled**
1 □	2	3	4	5

To score the ACT

Each response to the 5 ACT questions has a point value from a 1 to 5 as

shown on the form.To score the ACT, add up the point values for each response to all five questions.

SUBJECTIVE RATING OF ASTHMA CONTROL BY THE PATIENT SINCE PREVIOUS VISIT

Baseline

…….

0% **50%** **100%**

1st visit

…….

0% **50%** **100%**

2nd visit

…….

0% **50%** **100%**

3rd visit

…….

0% **50%** **100%**

USE OF RESCUE MEDICATION

NEED FOR RESCUE MEDICATION IN THE PAST 4

WEEKS

1ST VISIT

2ND VISIT

3RD VISIT

SPIROMETRIC PARAMETERS

A] SPIROMETRIC RESULTS AT THE BASELINE
DATE:

PARAMETERS PREDICTED PREBD %PREDICTED POST-BD %CHANGE

FVC

FEV1

FEV1 %

PEFR

B] SPIROMETRIC RESULTS AT THE END OF 4 WEEKS
DATE:

PARAMETERS PREDICTED ACTUAL %PREDICTED

FVC

FEV1

FEV1 %

PEFR

C] SPIROMETRIC RESULTS AT THE END OF 8 WEEKS
DATE:

PARAMETERS PREDICTED ACTUAL %PREDICTED

FVC

FEV1

FEV1 %

PEFR

D] SPIROMETRIC RESULTS AT THE END OF 12 WEEKS DATE:

PARAMETERS PREDICTED ACTUAL %PREDICTED

FVC

FEV1

FEV1 %

PEFR

LABORATORY INVESTIGATIONS

INVESTIGATIONS	BASELINE	AT THE END OF STUDY
COMPLETE HAEMOGRAM		
Hb		
RBC Count		
WBC Count		
Platelet Count		
RENAL FUNCTION TESTS		
S.Creatinine		
Blood urea		
LIVER FUNCTION TESTS		
SGOT		
SGPT		
CT		
BT		
Random Blood Sugar		
Chest X-		

ஆஸ்துமா கட்டுப்பாடு வினாக்கள்

1. கடந்த நான்கு வாரங்களில் உங்கள் பணியிடம், பள்ளி அல்லது வீட்டில் வேலைக்காகச் செலவிடும் நேரத்தில் எவ்வளவு நேரத்தை உங்களது ஆஸ்துமா (இளைப்பு நோய்) எடுத்துக்கொள்கிறது?

   (1) எல்லா நேரமும்
   (2) பெரும்பாலான நேரம்
   (3) சில நேரம்
   (4) மிகக் குறைந்த நேரம்
   (5) ஒரு போதும் இல்லை

2. கடந்த நான்கு வாரங்களில் எத்தனை முறை உங்களுக்கு மூச்சு இறைப்பு (மூச்சு விடுவதில் சிரமம்) ஏற்பட்டது?

   (1) ஒரு நாளில் ஒரு முறைக்கு மேல்
   (2) ஒரு நாளில் ஒரு முறை
   (3) ஒரு வாரத்தில் மூன்று முதல் ஆறு முறை
   (4) ஒரு வாரத்தில் ஒன்று அல்லது இரண்டு முறை
   (5) ஒரு போதும் இல்லை

3. கடந்த நான்கு வாரங்களில் எத்தனை முறை உங்களது ஆஸ்துமா நோயின் அறிகுறி (இளைப்பு, இருமல் , மூச்சு விடுவதில் சிரமம், நெஞ்சு கனம் அல்லது வலி) உங்களை இரவிலோ அல்லது வழக்கமாகக் காலை எழும் நேரத்திற்கு முன்போ விழித்தெழும்படி செய்கிறது?

   (1) ஒரு வாரத்தில் நான்கு அல்லது மேற்பட்ட இரவுகளில்
   (2) ஒரு வாரத்தில் இரண்டு அல்லது மூன்று இரவுகளில்
   (3) ஒரு வாரத்தில் ஒரு முறை
   (4) நான்கு வாரங்களில் ஒன்று அல்லது இரு முறை
   (5) ஒரு போதும் இல்லை

4. கடந்த நான்கு வாரங்களில் எத்தனை முறை நீங்கள் நிவாரண இன்ஹேலர் (தங்ள்ஸ்ரீன்ங் ஐய்ட்ஹப்ங்ழ்) அல்லது நெபுலைசர் (சஹசஷ்ன்ப்ண்சஷ்ங்ழ்) பயன்படுத்தினீர்கள்?

(1) ஒரு நாளில் மூன்று அல்லது அதற்கு மேலான முறை
(2) ஒரு நாளில் ஒன்று அல்லது இரண்டு முறை
(3) ஒரு வாரத்தில் இரண்டு அல்லது மூன்று முறை
(4) ஒரு வாரத்தில் ஒரு முறை
(5) ஒரு போதும் இல்லை

5. கடந்த நான்கு வாரங்களில் உங்களது ஆஸ்துமா நோய் எந்த அளவிற்கு கட்டுப்பட்டதாக மதிப்பிடுகிறீர்கள்?

(1) முற்றிலும் கட்டுப்படவே இல்லை
(2) மிகக் குறைந்த அளவே கட்டுப்பட்டது.
(3) ஓரளவு கட்டுப்பட்டுள்ளது.
(4) நன்றாக கட்டுப்பட்டுள்ளது.
(5) முற்றிலும் கட்டுப்பட்டுள்ளது.

ANNEXURE II

INFORMED CONSENT FORM

Title of the study : Efficacy, safety and cost effectiveness of oral Doxofylline and Theophylline for mild to moderate persistent bronchial asthma:

A randomized retrospective open labeled comparative study.

Name of the Participant

Name of the Principal, Co-Investigator: Dr.M.Nandhini Priya, Dr.Purushothaman

Name of the Institution: The Chengalpattu Medical College

Name and address of the sponsor / agency (ies) (if any): Nil

Documentation of the informed consent

I _____ have read the information in this form (or it has been read to me).I was free to ask any questions and they have been answered. I am over 18 years of age and, exercising my free power of choice, hereby give my consent to be included as a participant in Efficacy, safety and cost effectiveness of oral Doxofylline and Theophylline for mild to moderate persistent bronchial asthma- a randomized prospective open labeled comparative study

1. I have read and understood this consent form and the information provided to me.
2. I have had the consent document explained to me.
3. I have been explained about the nature of the study.
4. I have been explained about my rights and responsibilities by the investigator.
5. I have been informed the investigator of all the treatments I am taking or have taken in the past_____ months including any native (alternative) treatment.
6. I have been advised about the risks associated with my participation in this study.*****
7. I agree to cooperate with the investigator and I will inform him/her immediately if I suffer unusual symptoms.*****
8. I have not participated in any research study within the past _____month(s).*****
9. I have not donated blood within the past _____ months—Add if the study involves Extensive blood sampling. *****
10. I am aware of the fact that I can opt out of the study at any time without having to give any reason and this will not affect my future treatment in this hospital. *****
11. I am also aware that the investigator may terminate my participation in the study at any time, for any reason, without my consent. *****
12. I hereby give permission to the investigators to release the information obtained from me as result of participation in this study to the sponsors, regulatory

authorities, Govt. agencies, and IEC. I understand that they are publicly presented.

13. I have understand that my identity will be kept confidential if my data are publicly presented
14. I have had my questions answered to my satisfaction.
15. I have decided to be in the research study. I am aware that if I have any question during this study, I should contact the investigator. By signing this consent form I attest that the information given in this document has been clearly explained to me and understood by me, I will be given a copy of this consent document

For adult participants:

Name and signature / thumb impression of the participant (or legal representative

if participant incompetent)

Name _____ Signature_____ Date_____

Name and Signature of impartial witness (required for illiterate patients)

Name _____ Signature_____ Date_____

Address and contact number of the impartial witness

ஒப்புதல் படிவம்

திரு/திருமதி.....

.....

.....

.....

விலாசத்தில் வசிக்கும் நான், எனக்கு அளிக்கப்பட்ட தகவல் படிவத்தில் உள்ள விசயங்களை படித்தும் , கேட்டும் புரிந்து கொண்டேன்.

இந்த ஆய்வு மருத்துவர்.மு.நந்தினிபிரியா அவர்களால், அனுபவம் வாய்ந்த மருத்துவர்களின் உதவியோடு செங்கல்பட்டு அரசு மருத்துவமனை, நெஞ்சக நோய் சிகிச்சை பிரிவில் நடத்தப்படுகிறது என்பதை அறிவேன்.

இந்த ஆய்விற்கு தேவையான அனைத்து பரிசோதனைகளும் (இரத்த பரிசோதனை உட்பட) செய்துகொள்ள சம்மதிக்கிறேன்.

ஆய்வில் தொடர்ந்து பங்குபெற விருப்பம் இல்லை என்றால் விலகிக் கொள்ளலாம் என்றும் அறிந்துக் கொண்டேன்.

ஆய்வின் முடிவினை சொந்த அடையாளங்களை வெளியிடாமல் மருத்துவ ஆராய்ச்சிக்காக பயன்படுத்திக் கொள்ள சம்மதிக்கிறேன்.

நாள்: கையொப்பம்:

இடம்: பெயர்:

ANNEXURE III

Information to Participants

Sponsor: Nil

Investigator (principal and at least one Co-investigator): Dr.M.Nandhini Priya, Dr.Purushothaman

Name of Participant

Title: Efficacy, safety and cost effectiveness of oral Doxofylline and

Theophylline for mild to moderate persistent bronchial asthma: A randomized

prospective open labeled comparative study. You are invited to take part in this research/ study /procedures. The information in this document is meant to help you decide whether or not to take part. Please feel free to ask if you have any queries or concerns.

You are being asked to participate in this study being conducted in __ Chengalpattu Medical College

Purpose of the Research

Bronchial asthma is a chronic inflammatory disorder characterized by airway hyper responsiveness that leads to recurrent episodes of wheezing, breathlessness, chest tightness, and coughing particularly at the night or early morning. Often associated with variable, widespread obstruction that is reversible either spontaneously or with treatment1,2.

We want to test the efficacy and safety of a new drug in these diseases

We have obtained permission from the Institutional Ethics Committee

The Study Design

The study subjects will be randomly allocated into two groups of 60 patients each. Demographic data, history, clinical examination and details of drug prescription by the treating physician will be recorded in the study proforma. Group 1 patients will be treated with Doxofylline 400mg once daily and group 2 patients will be treated with Theophylline twice daily. The patients will be followed for 12 weeks. Relevant lab investigations will be done at the beginning and at the end of the study. The schedule of patient visit is as follows Visit 1/ day1 / initial or baseline assessment and follow-up at 4, 8 & 12 weeks.

At each visit, the study physician will examine you. Some test will be carried out at each visit. Blood collection involves prick with a needle and syringe.

In addition, if you notice any physical or mental changes, you must contact the persons listed at the end of the document. [You will be required to return unused study medicines when you report for your scheduled visits. This will enable correct assessment of the study results.]You may have to come to the hospital (study site) for examination and investigations apart from your scheduled visits, if required.

Confidentiality of the information obtained from you

You have the right to confidentiality regarding the privacy of your medical information (personal details, results of physical examinations, investigations, and your medical history). By signing this document, you will be allowing the research team investigators, other study personnel, sponsors, IEC and any person or agency required by law like the Drug Controller General of India to view your data, if required. The information from this study, if published in scientific journals or presented at scientific meetings, will not reveal your identity.

Possible benefits to other people

The result of the research may provide benefits to the society in terms of advancement of medical knowledge and/or therapeutic benefits to future patients.

How will your decision to not participate in the study affect you?

Your decisions to not participate in this research study will not affect your medical care or your relationship with investigator or the institution. Your doctor will still take care of you and you will not loose any benefits to which you are entitled.

Can you decide to stop participating in the study once you start?

The participation in this research is purely voluntary and you have the right to withdraw from this study at any time during course of the study without giving any reasons. However, it advisable that you talk to the research team prior to Stopping the treatment.

தகவல் படிவம்

செங்கல்பட்டு அரசு மருத்துவமனை, நெஞ்சக நோய் சிகிச்சை பிரிவில் டாக்ஸோபைலின் என்ற மருந்தின் ஆஸ்துமா நோயை கட்டுப்படுத்தும் தன்மை குறித்து ஆய்வு நடத்தப்படுகிறது.

இந்த ஆய்வு மருத்துவர் மு.நந்தினிபிரியா அவர்களால் அனுபவம் வாய்ந்த மருத்துவர்களின் உதவியோடு நடத்தப்படுகிறது.

டாக்ஸோபைலின் மருந்தினை 400 மில்லிகிராம் அளவில் தினமும் உட்கொள்ளும்போது , ஆஸ்துமா நோயின் தீவிரத்தை கட்டுப்படுத்தப்படுவதாக ஆய்வுகளில் கண்டறியப்பட்டுள்ளது. மேலும் இதன் பக்கவிளைவுகள் மிகவும் குறைவு மற்றும் ஆபத்தில்லாதது.

இந்த மருந்தின் ஆஸ்துமா நோயின் தீவிரத்தை கட்டுப்படுத்தும் தன்மை அறிவதற்காக ஒவ்வொரு மாதமும் ஸ்பைரோமெட்ரி பரிசோதனை மேற்கொள்ளப்படும். இந்த ஆய்வு 3 மாத காலம் நடத்தப்படும்.

இந்த ஆய்வில் பங்கேற்க முன்வந்தால் மட்டுமே கலந்து கொள்ள முடியும்.

DOXOFYLLINE GROUP

History and general examination

S.NO.	AGE	SEX	OCCUPATION	DURATION OF ILLNESS	AGE RAATDING FACTORS	FAMILY HISTORY	BMI
1	40	M	TAILOR	4	DUST	-	20.1
2	59	M	-	10	COLD WEATHER	BA	21.2
3	58	M	-	12	COLD WEATHER	-	19.4
4	50	M	MILK VENDER	10	DUST	ALLERGY	20.6
5	57	M	SECURITY	4	DUST	-	21.4
6	46	M	CARPENTER	8	DUST	-	19.8
7	52	F	-	10	COLD WEATHER	-	29.4
8	54	M	AGRICULTURE	15	DUST	-	19.9
9	47	F	-	10	COLD WEATHER	BA	21.4
10	35	F	CONSTRUCTION WORKER	3	DUST	-	22.3
11	41	F	HOUSEMAID	5	DUST	-	20.6
12	52	M	SHOP KEEPER	7	DUST	-	21.5
13	37	F	CLERK	5	-	-	22.7
14	56	F	-	10	COLD WEATHER	BA	28.6
15	39	M	CIVIL CONSTRUCTION WORKER	4	DUST	-	19.8
16	42	M	GARDENER	7	-	-	19.1
17	27	F	RECEPTIONIST	2	-	-	20.3
18	48	M	FACTORY WORKER	8	AIRPOLLUTION	-	21.5
19	42	M	AUTO DRIVER	3	-	-	22.7
20	37	F	AGRI COOLI	5	DUST	-	23.4
21	40	F	FISH SELLER	7	-	-	29.2
22	51	M	COOLI	6	-	-	19.6
23	27	M	MECHANIC	2	-	-	20.5
24	44	F	CONSTRUCTION WORKER	10	DUST	BA	21.7
25	38	F	-	3	-	-	22.9
26	54	F	-	8	COLD WEATHER	BA	28.1
27	54	M	SHOP WORKER	6	-	-	19.2
28	39	M	FISHERMAN	7	-	-	19.6
29	47	M	CABLE OPERATOR	5	-	-	20.4
30	49	M	AGRI COOLI	10	DUST	-	21.8

DOXOFYLLINE GROUP

History and general examination

S.NO.	AGE	SEX	OCCUPATION	DURATION OF ILLNESS	AGE RAATDING FACTORS	FAMILY HISTORY	**BMI**
31	52	F	VEGETABLE VENDER	12	COLD WEATHER	BA	27.4
32	42	M	AUTO DRIVER	7	-	-	19.2
33	53	F	HOUSEMAID	10	DUST	-	18.4
34	47	M	CONSTRUCTION COOLI	10	DUST	-	18.6
35	35	F	CLERK	3	DUST	-	18.2
36	56	F	-	10	COLD WEATHER	BA	19.4
37	42	M	CONSTRUCTIO WORKER	7	DUST	-	20.8
38	41	F	HOUSE MAID	4	DUST	-	21.7
39	50	F	HOUSE MAID	7	DUST	-	20.6
40	48	M	FACTORY WORKER	8	AIR POLLUCTION	-	22.3
41	47	M	DRIVER	10	COLD WEATHER	BA	19.3
42	33	F	TEA STALL	2	DUST	-	18.8
43	49	M	AGRICULTURE FORMER	9	DUST	-	19.4
44	54	F	-	12	COLD WEATHER	BA	28.8
45	39	M	MECHANIC	5	DUST	BA	19.2
46	42	M	PETROL BUNK	7	AIR POLLUCTION	-	20.4
47	48	M	CONTRUCTION WORKER	8	DUST	-	18.6
48	36	F	-	3	DUST	-	22.4
49	29	M	PAINTER	2	AIR POLLUCTION	-	19.1
50	39	F	AGRI COOLI	8	DUST	BA	18.8
51	42	M	HOTEL SERVICE	12	COLD WEATHER	BA	21.4
52	55	F	-	15	COLD WEATHER	BA	29.4
53	49	M	MILK VENDER	4	DUST	-	19.7
54	38	F	GROSSARY SHOP	2	DUST	-	20.1
55	47	M	FACTORY WORKER	10	AIR POLLUCTION	-	18.6
56	52	M	FARMER	12	DUST	BA	22.6
57	43	F	CATTLE REARING	8	DUST	-	19.8
58	47	M	GARDENER	4	DUST	-	20.2
59	40	F	SHOP KEEPER	3	DUST	-	19
60	52	M	SECURITY	3	COLD WEATHER	-	22.8

DOXOFYLLINE GROUP

History and general examination

S.NO.	AGE	SEX	OCCUPATION	DURATION OF ILLNESS	AGE RAATDING FACTORS	FAMILY HISTORY	BMI
61	40	M	CARPENTER	7	DUST	-	24.1
62	53	F	VEGETABLE VENDER	10	COLD WEATHER	BA	28.1
63	44	M	ELECTRICIAN	8	DUST	-	23.4
64	47	M	PETROL BUNK	2	AIR POLLUCTION	-	21.2
65	36	F	-	3	DUST	-	22.1
66	54	F	FISH VENDER	6	DUST	-	18.6
67	50	M	LAUNDRY	10	-	-	19.2
68	43	F	HOUSE MAID	5	-	-	18.8
69	37	M	GARDENER	3 yrs	DUST	-	18.2
70	42	M	DOBHI	10 yrs	DUST	Yes (BA)	21.4
71	38	M	CONSTRUCTION WORKER	3 yrs	DUST	-	17.8
72	45	F	-	4 yrs	-	-	24.6
73	57	M	-	10 yrs	COLD WEATHER	Yes (BA)	19.2
74	59	M	-	12 yrs	COLD WEATHER	Yes (BA)	18.4
75	50	M	LAUNDRY WORKER	15 yrs	AIR POLLUCTION	-	23.2
76	52	M	AGRI COOLI	12 yrs	DUST / COLD WEATHER	Yes (BA)	20.1
77	49	M	SHOPKEEPER	4 yrs	DUST	-	29.6
78	40	M	FACTORY WORKER	6 yrs	AIR POLLUCTION	-	21.2
79	42	M	SECURITY	4 yrs	COLD WEATHER	-	19.8
80	38	M	HOUSE MAID	5 yrs	DUST	-	18.2

BA-bronchial Asthma
BMI-Body

DOXOFYLLINE GROUP

Efficacy and safety

S.NO.	ACT SCORE				SUBJECTIVE RATING				FVC % PREDECTED				FEV 1				PEFR				FEV 1/FVC				ADRS
	0	1	2	3	0	1	2	3	0	1	2	3	0	1	2	3	0	1	2	3	0	1	2	3	
1	15	16	20	21	45	60	75	85	58	64	72	80	59	70	72	71	59	70	68	70	64	67	71	73	
2	17	18	19	23	55	55	80	80	62	68	80	83	61	66	71	72	58	71	65	78	60	62	68	81	
3	15	16	20	22	45	65	75	85	60	67	74	80	60	68	72	60	64	66	74	75	63	72	74	75	NAUSEA
4	16	17	21	21	45	70	70	85	63	71	81	82	58	64	65	61	61	72	72	72	62	71	77	72	
5	15	16	21	23	50	60	80	80	55	70	76	81	62	67	60	72	60	72	71	81	65	62	68	87	
6	16	17	19	21	50	60	75	85	62	68	72	79	58	66	68	73	58	60	70	73	61	68	76	82	
7	17	19	20	22	55	65	80	80	64	71	74	80	61	68	74	75	58	67	69	75	66	61	73	71	
8	15	18	19	23	45	60	75	90	61	70	78	83	60	64	75	72	59	66	75	81	64	63	79	76	
9	15	16	20	22	45	65	80	85	63	68	80	82	58	66	71	82	62	70	74	81	62	60	76	80	
10	17	19	21	21	55	55	75	90	65	71	76	81	62	65	70	70	63	62	65	72	60	68	63	72	
11	16	18	18	23	50	65	70	80	60	68	73	80	60	64	71	73	62	62	67	73	66	69	74	74	
12	17	19	20	21	55	60	70	85	55	72	78	80	61	69	72	72	64	66	74	75	63	61	75	72	
13	16	17	19	22	50	65	80	80	61	70	74	84	61	67	75	75	61	61	75	71	63	61	73	74	EPI GASTRIC PAIN
14	17	17	21	23	55	70	70	85	58	68	72	82	59	66	74	70	60	71	63	73	66	65	75	74	
15	15	18	18	21	45	65	75	80	63	66	80	80	58	65	72	73	61	67	69	76	65	70	76	70	
16	16	19	19	22	50	60	80	90	60	68	76	81	59	68	73	86	59	72	73	74	62	63	68	73	
17	17	17	20	23	55	55	70	85	62	70	81	85	61	64	71	72	59	66	75	72	60	64	71	73	
18	16	18	18	21	50	65	80	80	55	72	78	80	60	65	65	82	58	68	67	72	63	68	72	81	
19	17	17	19	22	55	60	75	90	58	68	75	79	59	66	72	83	63	70	79	82	61	65	68	72	
20	15	16	18	23	45	65	70	85	60	66	74	78	58	68	70	83	63	72	71	81	64	69	78	75	
21	17	19	21	21	55	60	80	80	63	68	72	81	62	68	74	85	64	70	74	75	64	68	73	72	
22	16	17	18	22	50	70	70	90	76	67	80	82	60	64	75	73	62	69	72	75	65	68	69	74	
23	15	16	21	21	45	55	80	80	61	72	78	80	61	69	78	83	60	69	79	76	61	71	76	81	
24	15	18	19	23	45	65	75	90	55	68	76	79	61	69	70	82	61	72	70	72	60	63	78	70	
25	17	19	20	22	55	60	80	85	50	70	82	86	58	64	70	70	61	62	77	73	65	64	68	72	
26	16	17	21	23	50	70	70	90	58	66	74	80	59	66	71	71	58	71	76	75	64	70	79	84	EPI GASTRIC PAIN
27	15	16	18	21	45	65	80	80	50	72	75	81	62	69	72	70	59	69	75	71	60	66	76	81	
28	17	18	19	22	55	60	75	85	63	67	78	83	60	70	75	73	64	67	71	74	63	62	73	72	
29	16	17	21	23	50	55	70	80	64	71	72	78	61	70	76	84	62	66	74	72	62	61	74	78	
30	17	18	20	21	55	65	80	90	62	68	80	80	59	68	65	83	63	69	74	72	64	69	71	74	

DOXOFYLLINE GROUP

Efficacy and safety

S.NO.	ACT SCORE				SUBJECTIVE RATING				FVC % PREDECTED				FEV 1				PEFR				FEV 1/FVC				ADRS
	0	1	2	3	0	1	2	3	0	1	2	3	0	1	2	3	0	1	2	3	0	1	2	3	
31	15	17	18	23	45	60	75	90	60	69	74	81	59	66	75	84	61	60	73	74	66	68	68	79	
32	16	18	20	22	50	65	80	85	58	70	76	79	62	68	72	85	60	61	72	81	60	66	79	70	
33	15	16	19	21	45	60	75	80	60	67	72	84	61	69	74	86	59	65	70	76	65	65	75	83	
34	15	16	19	21	45	60	75	80	60	70	80	82	61	69	74	86	59	65	70	76	65	65	75	83	
35	15	17	22	22	45	55	75	80	62	65	75	81	60	69	71	84	64	67	68	70	61	69	75	75	
36	16	18	20	23	50	60	70	85	60	64	78	84	58	65	76	86	64	65	74	74	65	68	74	73	GIDDINESS
37	17	17	21	23	55	65	75	85	58	67	80	79	61	70	78	82	62	66	71	73	63	64	77	78	
38	16	18	22	22	50	60	70	90	58	70	79	81	60	66	75	85	60	63	65	80	60	63	75	74	
39	17	18	22	23	55	60	75	90	61	66	76	84	62	68	72	84	60	62	77	78	66	69	78	73	
40	16	18	20	21	50	65	70	90	60	67	79	82	61	65	72	72	58	69	75	80	62	66	80	70	
41	15	18	21	23	45	70	80	90	58	64	77	78	59	69	77	73	58	72	74	81	64	61	77	73	
42	16	17	22	22	50	65	75	85	59	70	79	78	60	68	76	84	60	67	76	71	65	67	75	83	
43	17	20	20	23	55	65	75	90	60	68	78	80	58	70	75	73	61	66	70	75	61	63	76	81	
44	17	20	21	22	55	70	80	90	62	64	80	83	62	69	74	83	59	71	71	72	63	69	79	80	
45	16	18	22	23	50	60	80	85	61	69	76	81	60	67	72	71	62	68	75	74	60	69	78	77	PALPITATION
46	16	20	20	21	0	65	75	85	58	70	74	84	61	64	72	84	60	71	74	76	62	67	80	72	
47	15	19	21	23	45	65	75	90	60	66	74	82	59	66	77	72	61	72	72	81	64	70	79	75	
48	16	20	22	22	50	60	70	85	61	66	76	79	59	64	74	86	59	68	75	82	63	68	77	73	
49	16	20	20	21	0	70	80	80	59	68	79	78	61	65	78	82	61	70	68	81	64	62	76	81	
50	15	18	21	22	50	70	80	80	62	67	77	81	62	69	75	84	62	71	65	77	63	60	68	80	
51	16	17	22	22	45	65	75	85	60	65	78	83	62	70	77	86	58	69	77	73	60	63	78	82	
52	15	20	20	21	45	60	80	90	62	68	78	84	60	66	71	85	61	62	71	82	64	66	76	76	
53	16	20	21	232	50	65	80	90	59	70	76	80	59	68	78	84	62	68	69	75	66	69	78	73	
54	15	19	22	22	45	65	80	90	59	64	75	81	59	65	80	72	60	61	75	81	61	71	79	77	
55	16	17	22	23	50	70	70	90	61	65	79	84	58	64	72	84	58	66	77	85	65	68	77	72	
56	17	19	20	21	55	70	75	85	62	69	74	79	58	67	77	82	62	64	71	86	63	70	73	73	GIDDINESS
57	15	20	22	22	45	70	85	90	60	66	75	83	61	66	75	84	59	66	74	82	62	72	68	76	
58	16	17	22	23	50	65	70	85	58	69	80	80	62	69	79	72	60	63	65	74	64	68	76	82	
59	17	19	21	22	55	65	80	90	59	67	79	82	60	65	78	85	59	72	76	83	61	69	69	79	
60	16	19	22	23	50	70	70	85	58	65	77	84	61	68	77	82	61	68	68	81	60	68	70	79	

DOXOFYLLINE GROUP

Efficacy and safety

S.NO.	ACT SCORE				SUBJECTIVE RATING				FVC % PREDECTED				FEV 1				PEFR				FEV 1/FVC				ADRS
	0	1	2	3	0	1	2	3	0	1	2	3	0	1	2	3	0	1	2	3	0	1	2	3	
61	15	19	20	21	45	70	80	90	61	67	75	83	59	64	72	72	60	70	77	86	64	66	79	84	
62	16	19	22	22	50	65	80	90	60	70	74	82	61	67	77	83	58	71	72	84	62	71	75	86	
63	17	20	22	23	55	65	75	85	62	64	79	83	58	66	72	74	62	69	71	73	63	69	80	83	
64	17	17	21	22	5	60	80	90	59	69	74	81	60	69	75	71	59	71	70	83	65	72	78	74	
65	16	19	20	21	50	65	75	85	59	65	76	82	62	66	78	73	62	68	70	85	66	69	71	79	
66	15	20	22	2	45	60	80	90	61	70	77	80	59	64	73	86	58	70	69	72	60	70	76	81	
67	16	17	22	23	50	70	75	85	60	69	79	83	58	70	75	83	61	71	74	81	62	72	71	75	
68	15	18	21	23	45	70	70	90	75	69	79	83	66	70	71	70	61	71	74	81	62	72	71	75	
69	19	19	20	21	70	70	80	85	62	70	77	84	60	64	72	73	62	70	79	82	64	69	78	83	
70	18	18	20	21	60	60	80	85	60	68	73	80	54	66	77	82	66	69	73	71	67	60	76	84	
71	17	18	19	20	60	16	70	80	64	71	75	79	60	68	70	74	64	72	70	73	62	62	72	81	
72	16	16	19	20	50	50	70	80	66	76	78	80	62	70	73	84	62	67	71	84	65	71	75	82	
73	17	18	18	20	60	60	60	80	61	72	76	81	58	69	72	76	60	69	74	83	63	61	78	78	
74	16	17	20	21	50	60	20	80	63	68	76	86	61	67	65	73	63	72	65	75	62	63	75	75	NAUSEA
75	16	16	20	20	50	50	80	80	58	68	75	82	58	68	72	86	58	68	68	82	60	69	73	76	
76	16	18	20	22	50	60	80	85	64	74	78	86	59	70	72	84	62	70	73	75	61	67	76	84	
77	15	16	16	18	40	50	50	60	58	64	72	80	58	66	74	80	56	66	74	74	63	66	69	85	
78	17	17	19	20	60	60	70	80	65	76	78	84	62	65	71	70	60	70	71	73	62	68	77	83	
79	16	17	19	20	50	60	70	80	62	68	78	86	61	71	71	84	59	71	71	86	63	69	78	84	
80	17	18	20	22	60	60	80	85	60	68	76	82	58	65	70	71	61	69	70	71	61	69	77	82	

ACT- Asthma control test
FVC-Force vital capacity
FEV1- Forced expiratory volume in one sec
PEFR-Peak expiratory flow rate
ADRS- Adverse drug reactions

DOXOFYLLINE GROUP

Cost effectiveness

S.NO.	DISTANCE FROM HEALTH FACILITY	LOSS OF WAGES		TRAVEL		FOOD		TOTAL ID	INV	DIRECT COSTS		TMT OF ADR	GRAND TOTAL
		PT	ACP	PT	ACP	PT	ACP			TMT	TOTAL		
1	7	200	-	30	-	20		250		267.12			517.12
2	2	-	200	20	20	20	20	280		267.12			547.12
3	4	-	150	20	20	20	20	230		267.12		12.13	509.25
4	6	100	-	30	-	20	-	150		267.12			417.12
5	12	100	-	40	-	30	-	170		267.12			437.12
6	8	200	-	30	-	20	-	250		267.12			517.12
7	7	-	-	30	-	20	-	50		267.12			317.12
8	15	150	-	60	-	70	-	280		267.12			547.12
9	13	-	100	40	40	30	30	240		267.12			507.12
10	3	70	-	20	-	20	-	110		267.12			377.12
11	5	100	-	30	-	20	-	150		267.12			417.12
12	7	150	-	30	-	20	-	200		267.12			467.12
13	9	500	-	30	-	20	-	550		267.12		2.95	819.77
14	11	-	-	40	-	30	-	70		267.12			337.12
15	13	100	-	40	-	30	-	170		267.12			337.12
16	15	100	-	60	-	70	-	230		267.12			297.12
17	17	500	-	60	-	70	-	630		267.12			897.12
18	19	200	-	70	-	100	-	370		267.12			637.12
19	20	200	-	70	-	100	-	370		267.12			637.12
20	18	50	-	60	-	70	-	180		267.12			447.12
21	16	100	-	60	-	70	-	230		267.12			497.12
22	14	70	-	40	-	30	-	140		267.12			407.12
23	12	150	-	40	-	30	-	220		267.12			487.12
24	6	70	-	30	-	20	-	120		267.12			387.12
25	8	-	140	30	30	20	20	240		267.12			507.12
26	10	-	-	40	-	30	-	70		267.12		2.95	340.07
27	4	100	-	20	-	20	-	140		267.12			407.12
28	2	200	-	20	-	20	-	240		267.12			507.12
29	3	100	-	20	-	20	-	140		267.12			407.12
30	7	50	-	30	-	20	-	100		267.12			367.12

DOXOFYLLINE GROUP

Cost effectiveness

S.NO	DISTANCE FROM HEALTH FACILITY	LOSS OF WAGES		TRAVEL		FOOD		TOTAL ID	INV	DIRECT COSTS		TMT OF ADR	GRAND TOTAL
		PT	ACP	PT	ACP	PT	ACP			TMT	TOTAL		
31	9	100	-	30	-	20	-	150		267.12			417.12
32	11	200	-	40	-	30	-	270		267.12			537.12
33	13	100	-	40	-	30	-	170		267.12			437.12
34	2	100	-	20	-	20	-	140		267.12			407.12
35	6	500	-	30	-	20	-	550		267.12			817.12
36	3	-	150	20	20	20	20	230		267.12			497.12
37	9	100	-	30	-	20	-	150		267.12			417.12
38	12	100	-	40	-	30	-	170		267.12			437.12
39	15	200	-	60	-	70	-	330		267.12			597.12
40	18	500	-	60	-	70	-	630		267.12			897.12
41	20	300	-	70	-	100	-	470		267.12			737.12
42	20	150	-	70	-	100	-	320		267.12			587.12
43	16	-	-	60	-	70	-	130		267.12			397.12
44	12	200	200	40	40	30	30	540		267.12			807.12
45	8	200	-	30	-	20	-	250		267.12			517.12
46	4	200	-	20	-	20	-	240		267.12			507.12
47	2	100	-	20	-	20	-	140		267.12			407.12
48	3	-	500	20	20	20	20	580		267.12			847.12
49	5	200	-	30	-	20	-	250		267.12			517.12
50	7	50	-	30	-	20	-	100		267.12			367.12
51	9	100	-	30	-	20	-	150		267.12			417.12
52	11	-	200	40	40	30	30	340		267.12			607.12
53	13	100	-	40	-	30	-	170		267.12			437.12
54	15	100	-	60	-	70	-	230		267.12			497.12
55	14	200	-	40	-	30	-	270		267.12			537.12
56	17	150	-	60	-	70	-	280		267.12			547.12
57	19	200	-	60	-	70	-	330		267.12			597.12
58	3	100	-	20	-	20	-	140		267.12			407.12
59	7	100	-	30	-	20	-	150		267.12			417.12
60	6	100	-	30	-	20	-	150		267.12			417.12

DOXOFYLLINE GROUP

Cost effectiveness

S.NO	DISTANCE FROM HEALTH FACILITY	LOSS OF WAGES		TRAVEL		FOOD		TOTAL ID	INV	DIRECT COSTS		TMT OF ADR	GRAND TOTAL
		PT	ACP	PT	ACP	PT	ACP			TMT	TOTAL		
61	5	200	-	20	-	20	-	240		267.12			507.12
62	8	100	200	30	30	20	20	400		267.12			667.12
63	2	200	-	20	-	20	-	240		267.12			507.12
64	4	200	-	20	-	20	-	240		267.12			507.12
65	6	100	-	30	-	20	-	150		267.12			417.12
66	3	150	-	20	-	20	-	200		267.12			467.12
67	11	200	-	40	-	30	-	270		267.12			537.12
68	12	100	-	40	-	30	-	170		267.12			437.12
69	2	100	-	20	-	20	-	140		267.12			407.12
70	5	100	-	30	-	0	-	150		267.12			417.12
71	8	100	-	30	-	20	-	150		267.12			417.12
72	20	-	-	70	-	100	-	170		267.12			437.12
73	8	-	200	0	30	20	20	300		267.12			567.12
74	16	-	150	60	60	70	70	410		267.12		12.13	689.12
75	19	150	-	60	-	70	-	280		267.12			547.12
76	12	50	-	40	-	30	-	120		267.12			387.12
77	11	100	-	40	-	30	-	170		267.12			437.12
78	17	200	-	60	-	70	-	330		267.12			597.12
79	20	100	-	70	-	100	-	270		267.12			537.12
80	15	100	-	60	-	70	-	230		267.12			497.12

PT-pationt
ACP-accompaning person
ID-indirect cost
TMT-treatment
ADR-adverse drug reaction
ECG-electro cardio graphy
CXR-chest ex-ray
HB-hemoclobin
TC-total count
RBS-random blood sugar
BT-bleading time
CT-clotting time

DOXOFYLLINE GROUP

Investigations

S.NO	ECG		CXR		HB %		TC		RBS		SERUM CERATININE		BL UREA		SGOT		SGPT		BT		CT	
	0	3	0	3	0	3	0	3	0	3	0	3	0	3	0	3	0	3	0	3	0	3
1	N	N	N	N	9.9	11.1	8340	7940	111	125	1.1	0.9	12.3	13.5	22.8	25.1	20	21	5	4.5	5.4	5.5
2	N	N	N	N	12.2	13	7935	7535	132	130	1	0.8	12	13.8	23	24.8	18	22	4.5	5.2	6	5.5
3	N	N	N	N	11.8	10.9	8890	8490	130	136	1	1.1	13.2	14	24.2	22.8	22	20	5.2	5.4	6.2	6.3
4	N	N	Hyperventilation	Hyperventilation	8.8	11.3	7137	6737	115	123	0.9	1	14	12.8	25	23.2	19	20	5.4	5	5.3	6
5	N	N	N	N	12.7	11.9	8769	8369	118	127	1	0.9	13.8	24	25.3	20	21	22	5	5.4	5.4	6.2
6	N	N	N	N	11.8	12.9	8964	8564	140	136	1.1	1.1	12.8	13.8	24	25.3	20	21	4.5	5	6	5.5
7	N	N	N	N	10.9	12.5	9002	8602	128	131	0.8	1	12.2	12.9	24.2	25	22	19	5.5	5.2	6	6.2
8	N	N	N	N	13	12.6	8433	8033	132	138	1	0.8	14	13.2	25	24.5	19	20	5	5.5	6.2	6.3
9	N	N	N	N	11.5	12.3	7762	7362	130	136	1.1	1	12.2	14	25.5	25.6	21	22	4.5	5.3	5.5	6
10	N	N	N	N	12.7	12.9	7346	6946	127	130	0.9	1	13.6	13.9	23	24.7	20	18	5.2	4.5	5.4	6.1
11	N	N	N	N	10.7	10.9	8347	7947	119	134	0.9	1.1	14	13.5	23	24.6	18	20	4.5	5	5.2	6
12	N	N	N	N	11	12.9	8879	8479	121	129	1	1.1	13.8	13	25.2	22.9	22	21	5	5.2	5.2	5.4
13	N	N	N	N	8.9	11.4	7943	7543	140	137	1.1	0.9	13	14	25.5	24	19	20	5.1	5.2	6	5.5
14	N	N	N	N	10.6	12.8	7811	7411	132	129	1.1	0.8	14	12.8	24.8	25.2	21	19	4.5	4.5	6.1	6.3
15	N	N	N	N	11.5	12.1	8762	8362	129	140	0.8	1.1	13.6	13	23.7	25.4	20	18	5.2	5	5.4	6.1
16	N	N	N	N	12	12.9	7969	7569	120	129	1.1	1	12.9	13.4	22.8	23.8	18	21	5.5	5.1	6.2	5.5
17	N	N	N	N	11.3	11.9	8365	7965	119	130	0.8	1	12	13.7	22.3	24	19	22	5	5.3	5.4	6
18	N	N	N	N	12.2	13.1	8436	8036	122	138	0.9	0.8	13.8	12.7	22	24.7	22	20	4.5	5	6	6.2
19	N	N	N	N	11.9	12.3	8538	8138	137	140	1.1	0.8	13.3	14	22.8	23.2	18	19	5.2	5.5	5.4	6.1
20	N	N	N	N	10.7	11.8	7895	7495	133	136	1	1.1	14	13.5	25	25.8	20	21	5.5	4.5	5.5	6
21	N	N	N	N	9.8	12.3	7689	7289	131	129	0.9	1	13.9	13	25.2	24.2	21	22	4.5	5	5.3	6.3
22	N	N	N	N	10.2	3	8969	8569	127	133	0.8	0.9	12.8	12.1	23.7	24.6	19	20	5.2	5.4	6.1	6
23	N	N	N	N	10.9	12.7	7978	7578	121	139	1	1.1	12	13.4	22.6	22.9	22	21	5	5.5	5.4	6.2
24	N	N	N	N	11.7	12.9	7999	7599	118	128	1.1	1	12.8	13.3	22.3	23.3	20	22	5.5	4.5	6.2	5.5
25	N	N	N	N	10.6	9.9	8092	7692	134	127	1.1	0.8	13.2	14	23.3	25.1	18	22	5.3	5	5.5	6
26	N	N	N	N	12.1	13	8819	8419	117	129	1	0.9	13	13.8	23.8	24.9	21	20	5	5.2	6	6.2
27	N	N	N	N	13.1	11.8	7947	7547	115	126	1.1	1.1	13.5	12.9	25.2	24	19	22	4.5	5.4	6.2	6
28	N	N	N	N	11.7	10.8	8238	7838	122	132	0.9	1	13.4	13	24	25.5	18	21	5	5.4	5.4	6
29	N	N	N	N	12.1	12.9	8891	8491	123	133	0.9	1.1	13.1	13.8	25.2	25.6	21	20	5.3	5.2	6	5.4
30	N	N	N	N	12.6	12.1	8139	7739	134	140	1.1	1	14	13.5	25.5	25	22	21	5.4	5	5.3	5.5

DOXOFYLLINE GROUP

Investigations

S.NO	ECG		CXR		HB %		TC		RBS		SERUM CERATININE		BL UREA		SGOT		SGPT		BT		CT	
	0	3	0	3	0	3	0	3	0	3	0	3	0	3	0	3	0	3	0	3	0	3
31	N	N	N	N	12.4	11.9	7919	7519	129	136	1.1	0.9	12.9	12.8	23.3	24.2	20	22	5.5	4.5	6.2	6
32	N	N	N	N	10.9	12.1	7638	7238	139	132	0.8	1.1	13.7	13.8	23	25.6	18	21	5	5.2	6.1	6.2
33	N	N	N	N	11.8	12.5	8339	7939	125	133	0.9	1	13.2	14	22.8	24.6	19	21	4.5	5.3	5.3	6
34	N	N	N	N	11.7	13	7878	7478	137	130	1.1	0.9	12.9	13.2	22.6	24.3	21	19	5.5	5	6.1	6.2
35	N	N	N	N	8.2	10.1	8113	7713	119	131	0.9	1	13	12.8	23.8	24	18	20	5	5.5	5.3	6
36	N	N	N	N	9	11.2	7980	7580	137	129	1.0	1.1	13.8	12.9	22.6	25.5	22	22	4.5	5	5	5.4
37	N	N	N	N	9.7	12.1	8139	7739	126	130	1.0	1.1	12.9	13.2	24.5	25	19	20	5.5	5	5.2	6.2
38	N	N	N	N	12.1	13	8049	7649	120	129	0.9	0.8	14	13.8	25.1	25.5	21	22	5	4.5	6	5.4
39	N	N	N	N	13	12.8	7899	7499	134	140	0.8	1	13.2	13.5	22.9	23.6	18	20	5.3	4.5	6.2	6
40	N	N	N	N	12.8	11.9	8012	7612	130	139	0.9	1.1	12.8	13.3	25	25.6	19	18	5.1	5.2	5.4	5.3
41	N	N	N	N	11.9	10.1	8685	8285	126	135	0.8	0.9	14	13.7	24.8	25.1	22	18	5	5.2	6	6.2
42	N	N	N	N	13.1	10.7	8018	7618	128	138	1.1	1	13.5	13.9	24.4	23.8	20	19	5.4	5	6.2	5.4
43	N	N	N	N	12.7	9.8	8139	7739	119	130	0.8	1.1	12.5	13.6	23.9	24	20	21	5.5	5.2	5.5	5.3
44	N	N	N	N	9.9	10.2	8016	7616	116	137	1.0	1.1	12.8	13	25	25.5	18	22	5	5.5	5.2	5.5
45	N	N	N	N	10.1	11.11	7981	7581	140	138	1.1	0.9	13.9	14	24.5	24	18	20	4.5	5.2	6	6.2
46	N	N	N	N	12.7	13	8806	8406	129	133	0.8	1	13.2	13.6	25.5	23.6	19	21	5.2	5	6.2	5.3
47	N	N	N	N	11.7	12.4	7899	7499	130	139	0.9	0.8	13	13.9	23.2	25	22	20	5.58	5.5	5.3	5.5
48	N	N	N	N	10.8	12.1	8196	7796	126	140	1.0	1.1	12.7	14	23.8	25.2	20	19	5	4.5	6.1	6
49	N	N	N	N	10.2	11.8	7980	7580	128	137	1.1	1	12.5	12.9	24.6	24.4	21	18	5.3	5	5.5	6.2
50	N	N	N	N	11	12.1	7128	6728	131	139	0.9	1.1	13.1	13.5	24.2	25.3	18	21	4.5	5.2	5.1	6
51	N	N	N	N	12.3	12.7	8026	7626	129	140	0.9	1	14	13.3	24	25.2	19	22	5.2	5.4	6	6.3
52	N	N	N	N	12.9	12.5	7751	7351	139	130	1.0	0.8	13.6	13	25.2	25	22	20	5.5	5	6.2	5.5
53	N	N	N	N	11.8	11.3	8321	7921	127	133	1.1	1	12.9	12.8	25	25.4	20	22	5	5.1	5.4	6.2
54	N	N	N	N	10.2	11.1	7892	7492	135	138	0.9	1.1	14	13.9	25.3	25	18	20	4.5	5.4	5.2	5.5
55	N	N	N	N	11.1	12.9	8105	7705	136	140	0.8	1.1	13.8	13.3	25.1	23.8	21	19	5.2	4.5	6	6.1
56	N	N	N	N	10.4	11.6	8211	7811	132	133	1.0	1	12.9	14	22.8	24.5	19	20	5.3	5.2	5.5	6
57	N	N	Hyperventilation	Hyperventilation	12.6	12.7	7971	7571	129	120	1.1	1	12.5	13.5	23.6	25	22	20	4.5	5	6.2	6
58	N	N	N	N	12.1	12.3	7734	7334	131	138	0.9	0.8	13.5	13	23.4	25.2	18	22	5	5.5	5.2	6.2
59	N	N	N	N	12	13	7032	6632	125	132	0.8	1.1	13.2	13.9	25.2	23.9	21	20	5.5	5.3	5.4	69
60	N	N	N	N	13.1	12.7	7996	7596	129	139	1.1	1	13	14	22.8	24.2	22	20	5	5.4	6	5.4

DOXOFYLLINE GROUP

Investigations

S.NO	ECG		CXR		HB %		TC		RBS		SERUM CERATININE		BL UREA		SGOT		SGPT		BT		CT	
	0	3	0	3	0	3	0	3	0	3	0	3	0	3	0	3	0	3	0	3	0	3
61	N	N	N	N	11.9	12.3	8055	7655	140	135	1.0	0.9	12.9	13.8	23	25.2	19	21	5.4	5	6.2	5.5
62	N	N	N	N	11.2	11.9	8091	7691	129	136	1.1	0.8	12.7	13.4	23.2	25	21	22	5.1	5.2	5.5	5.3
63	N	N	N	N	12.1	11.2	7998	7598	132	139	0.9	0.8	13.1	13.8	24.8	25.2	20	22	5	4.5	5.2	6
64	N	N	N	N	12.9	13	7539	7139	138	127	1.0	1.1	13.3	14	25	24.8	22	20	4.5	5	6	6.2
65	N	N	N	N	10.8	11.6	8113	7713	130	123	1.1	1	13.5	12.9	25.2	23.9	19	18	5.4	5.2	5.3	6.1
66	N	N	N	N	11.7	12.2	7946	7546	140	129	0.8	1	12.8	12	25.1	25.2	20	19	5.5	5	5.5	6.2
67	N	N	N	N	12.1	11.8	8981	8581	133	120	1.0	0.8	12.7	12.9	22.9	24.8	18	20	5	5.3	6.1	5.5
68	N	N	N	N	11	12.1	7989	7589	126	132	0.9	1	12.9	13.3	24.6	25.2	20	18	4.5	5.5	6	6.2
69	N	N	N	N	9.8	11.2	8430	8030	131	139	0.9	0.8	12	13.2	25.2	25	22	20	4.5	5	6.1	55
70	N	N	N	N	10.1	12.4	7962	7562	129	120	1.1	0.9	12.9	13.5	24.8	25.2	20	19	5	4.5	5.5	6
71	N	N	N	N	11.8	13	8705	8305	137	140	1.0	1.1	14	13.3	22.8	23	19	18	5.5	5	6	6.2
72	N	N	N	N	9.2	10.8	8103	7703	129	134	1.1	1	13.3	13	25	24.5	19	20	5.2	5	6.2	5.5
73	N	N	N	N	10.5	11.2	8187	7787	130	136	0.9	1	12.2	13.8	24.6	24	22	21	4.5	5.2	5.3	6.1
74	N	N	N	N	12.1	13	7985	7585	122	131	0.8	1.1	12.8	14	23.2	24.8	21	22	5.3	4.5	5.5	6
75	N	N	N	N	11.9	12.5	8112	7712	129	120	1.0	1.1	13.2	13.6	22.8	23.6	18	19	5.4	5	6	6.3
76	N	N	N	N	9.8	10.9	7985	7585	139	140	1.0	0.9	14	13.1	25.2	25	20	19	5	5.4	5.2	5.5
77	N	N	N	N	11.3	12.2	8531	8131	137	133	0.8	1	13.5	13.8	25.4	25.6	21	22	5.5	4.5	6	6.2
78	N	N	N	N	12	12.7	7935	7535	138	129	1.1	0.9	13	12.8	25	25.8	19	20	5.1	5.4	5.5	5.2
79	N	N	N	N	11.1	12.3	7632	7232	140	131	1.0	0.8	13.1	13.6	22.8	24.8	22	19	5.5	4.5	6.2	6
80	N	N	N	N	10	11.8	8136	7736	128	136	1.1	0.8	12.8	13.7	23.1	22.8	18	21	4.5	5	6	5.5

DERIPHYLLINE GROUP

History and general examination

S.NO.	AGE	SEX	OCCUPATION	DURATION OF ILLNESS	AGE RAATDING FACTORS	FAMILY HISTORY	BMI
1	58	M	NIL	17	DUST	NO	1
2	42	M	CATTLE REARING	5	DUST/CIGG SMOKE	NO	2
3	56	M	NIL	10	NIL	NIL	3
4	38	M	AGRI COOLI	20	DUST/COLD WEATHER	YES(BA)	4
5	59	M	NIL	6	DUST/SMOKE	NIL	5
6	35	F	WAITER IN COFFEE SHOP	2	DUST/AIR POLLUTION	YES(BA)	6
7	55	M	SECURITY	5	COLD WEATHER	NO	7
8	40	F	NIL	10	DUST/SMOKE	YES(ALER)	8
9	54	M	NIL	7	DUST/SMOKE	YES(BA)	9
10	30	F	AGRI COOLI	12	DUST/WEATHER	YES(BA)	10
11	58	M	NIL	10	DUST/SMOKE	NIL	11
12	48	F	NIL	5	DUST/SMOKE	NIL	12
13	50	M	AGRICULTURE	3	DUST/SMOKE	YES	13
14	37	F	CONTRUCTION COOLI	25	DUST/COLD WEATHER	YES(BA)	14
15	55	F	AGRI COOLI	15	COLD WEATHER	NIL	15
16	56	F	NIL	8	COLD WEATHER	NIL	16
17	32	F	NIL	1	DUST/SMOKE	YES	17
18	24	M	SECURITY	5	COLD WEATHER/ AIR POLLUTION	NO	18
19	36	F	NIL	3	DUST/SMOKE	YES(BA)	19
20	55	F	NIL	15	COLD WEATHER/DUST/SMOKE	NIL	20
21	50	F	AGRI COOLI	10	DUST/AIR POLLUTION	NIL	21
22	42	F	NIL	3	COLD WEATHER	YES(BA)	22
23	40	F	BUILDING(CIVIL COOLI WORK)	10	DUST/AIR POLLUTION	NIL	23
24	30	F	RECEPTIONIST	5	COLD WEATHER	YES(BA)	24
25	40	M	CLERK	10	DUST	NIL	25
26	22	M	STUDENT	7	DUST/COLD WEATHER	YES(BA)	26
27	55	M	CATTLE REARING	15	DUST/SMOKE	NIL	27
28	40	M	MECHANIC	8	DUST/AIR POLLUTION	NIL	28
29	38	F	HOUSE MAID	5	DUST/SMOKE	YES(BA)	29
30	27	M	CONTRUCTION LABOUR	3	DUST/SMOKE	YES(BA)	30

DERIPHYLLINE GROUP

History and general examination

S.NO.	AGE	SEX	OCCUPATION	DURATION OF ILLNESS	AGE RAATDING FACTORS	FAMILY HISTORY	BMI
31	33	M	DRIVER	4	DUST/COLD WEATHER	NIL	26.2
32	50	M	SECURITY	7	DUST/COLD WEATHER	NIL	22.4
33	38	M	GROSSORY SHOP	8	DUST/AIR POLLUTION	NIL	24.8
34	36	F	HOUSE MAID	6	DUST/COLD WEATHER	YES(BA)	26.4
35	50	F	-	2	-	-	18.2
36	26	M	MECHANIC	2	DUST/AIR POLLUTION	ALLERGY	17.6
37	38	M	TAILLOR	4	DUST	-	23.1
38	40	M	CIVIL WORKER	7	DUST/AIR POLLUTION	-	21.2
39	45	F	-	10	COLD WEATHER	BA	19.3
40	39	M	PAINTER	7	DUST/AIR POLLUTION	ALLERGY	20.4
41	28	F	HELPER IN SHOP	2	DUST/AIR POLLUTION	ALLERGY	17.6
42	52	M	CATTLE REARING	9	DUST	-	18.6
43	41	F	-	10	COLD WEATHER	-	18.4
44	46	F	AGRI COOLI	12	DUST/COLD WEATHER	-	19.6
45	52	M	CIVIL WORKER	8	DUST/AIR POLLUTION	ALLERGY	20
46	29	M	VEG VENDAR	3	-	-	21.7
47	55	F	-	12	COLD WEATHER	BA	24.6
48	49	M	MECHANIC	7	-	-	22.4
49	52	M	MILK VENDAR	15	DUST/AIR POLLUTION	ALLERGY	24
50	45	M	CLERK	10	DUST	-	22.3
51	56	M	-	20	COLD WEATHER	BA	26.2
52	28	F	CIVIL WORKER	3	DUST	-	16.2
53	46	M	SECURITY	10	COLD WEATHER	BA	19.4
54	38	M	FACTORY WORKER	6	AIR POLLUTION	-	17.6
55	52	F	CIVIL WORKER	12	DUST/AIR POLLUTION	-	18.9
56	37	M	CARPENTER	6	DUST	-	21.2
57	48	F	-	14	COLD WEATHER	BA	26.3
58	35	F	HOUSE MAID	5	DUST	-	30.2
59	46	M	HOTEL SERVER	9	COLD WEATHER	ALLERGY	22.4
60	53	M	-	10	COLD WEATHER	-	21.4

DERIPHYLLINE GROUP

History and general examination

S.NO.	AGE	SEX	OCCUPATION	DURATION OF ILLNESS	AGE RAATDING FACTORS	FAMILY HISTORY	BMI
61	55	F	-	12	DUST/AIR POLLUTION	ALLERGY	30.1
62	48	F	AGRI COOLI	11	DUST	-	24.6
63	49	M	SHOP KEEPER	10	DUST	-	28.2
64	52	M	CATTLE REARING	12	DUST	-	18.4
65	51	F	SHOP KEEPER	12	AIR POLLUTION	-	18.9
66	49	M	MILK VENDAR	10	DUST/AIR POLLUTION	ALLERGY	21.2
67	43	F	-	8	COLD WEATHER	BA	26.4
68	42	M	-	3	-	-	21.3
69	50	F	HOUSE MAID	10	DUST/COLD WEATHER	ALLERGY	18.6
70	42	M	OFF ATTENDER	7	DUST	-	19.2
71	38	F	-	8	COLD WEATHER	BA	21.4
72	59	M	-	12	DUST/COLD WEATHER	-	22.1
73	57	M	-	15	DUST/COLD WEATHER	BA	24
74	48	M	PETROL BUNK	7	DUST/AIR POLLUTION	-	16.8
75	58	M	-	12	COLD WEATHER	BA	21.4
76	52	F	HOUSE MAID	10	-	-	19.6
77	27	M	MECHANIC	2	-	-	18.3
78	37	F	FACTORY WORKER	5	DUST/AIR POLLUTION	-	22.7
79	43	M	CONDUCTOR	8	DUST	-	26.4
80	41	M	TEA SHOP	3	DUST	-	20.1

BA-bronchial Asthma
BMI-Body

DERIPHYLLINE GROUP

Efficacy and safety

S.NO.	ACT SCORE				SUBJECTIVE RATING				FVC % PREDECTED				FEV 1				PEFR				FEV 1/FVC				ADRS
	0	1	2	3	0	1	2	3	0	1	2	3	0	1	2	3	0	1	2	3	0	1	2	3	
1	16	18	20	20	60	70	70	80	55	78	80	82	50	68	74	79	68	70	74	76	64	68	76	78	PALPITATIONS
2	18	20	20	22	60	70	80	80	50	72	82	84	60	66	74	76	64	68	70	72	60	62	70	72	HEADACHE
3	18	20	20	21	50	60	70	80	45	68	70	80	58	60	74	78	58	62	68	74	58	62	70	74	TACHYCARDIA
4	19	20	21	22	70	70	80	80	55	82	82	86	55	74	76	80	72	74	80	80	68	70	70	81	INSOMNIA
5	16	18	18	20	50	60	60	70	60	64	70	82	59	62	70	76	60	64	68	72	59	60	68	70	NAUREA
6	15	17	16	18	50	60	60	65	65	62	72	78	58	60	72	76	56	60	66	76	60	63	69	75	VOMITING
7	15	16	16	18	50	50	60	70	50	64	70	79	58	62	69	73	60	64	70	78	62	64	74	80	TREMOR
8	16	18	20	20	60	60	70	70	40	72	80	82	53	68	78	80	67	70	78	78	68	70	78	76	EPIGASTRIC DISCOMFORT
9	18	18	20	22	60	60	70	80	50	72	78	82	62	64	72	74	62	64	70	72	62	64	72	74	HEADACHE
10	18	18	20	20	60	70	70	80	45	72	76	80	62	64	74	76	60	64	72	74	60	64	70	74	NAUSEA
11	16	16	18	20	50	60	60	70	64	68	72	74	52	64	72	78	58	62	68	76	60	63	70	76	TREMOR
12	16	16	18	20	50	60	70	70	65	66	70	74	62	64	74	78	60	65	75	80	62	64	72	78	EPIGASTRIC DISCOMFORT
13	18	18	20	22	60	60	70	80	54	74	79	82	64	66	78	80	68	70	76	78	64	68	76	78	TACHYCARDIA
14	17	17	19	20	50	60	70	70	50	64	72	76	50	66	74	76	58	64	70	76	58	62	74	76	TREMOR
15	17	16	20	20	60	50	70	70	64	58	72	77	66	60	74	78	64	60	72	76	64	60	76	78	HEADACHE
16	16	18	18	20	50	60	60	70	56	62	64	76	58	64	67	76	58	60	64	78	60	66	68	76	NAUREA
17	18	20	20	22	60	70	80	80	55	74	76	80	63	68	70	76	65	72	72	78	62	70	72	78	GIDDINESS
18	16	17	18	20	60	60	70	80	62	64	74	78	62	64	74	76	64	66	72	76	62	65	72	77	EPIGASTRIC DISCOMFORT
19	17	18	20	20	60	70	70	80	59	62	74	76	60	64	72	76	63	67	73	77	60	62	76	78	PALPITATIONS
20	18	20	20	22	70	70	80	80	68	66	76	80	64	66	78	80	64	68	76	79	64	66	72	78	HEADACHE
21	17	16	20	22	60	50	70	80	67	69	77	79	53	70	73	77	66	69	77	81	68	66	78	80	INSOMNIA
22	18	20	22	22	70	80	80	90	68	74	76	84	68	76	78	82	70	76	78	84	70	76	77	86	NAUREA
23	17	18	20	20	60	70	70	80	58	68	70	76	60	62	73	76	58	64	66	74	60	74	75	80	NAUREA
24	18	18	20	22	70	70	80	85	70	70	76	78	65	70	76	79	64	66	71	74	64	70	74	77	GIDDINESS
25	20	20	21	22	70	70	80	80	60	69	76	78	51	68	75	78	67	66	74	76	66	68	76	78	TREMOR
26	18	20	22	22	70	70	80	80	56	66	74	76	52	66	73	78	64	66	76	78	66	68	72	78	TREMOR
27	16	18	18	20	60	70	70	75	58	68	72	76	60	66	71	74	62	68	70	72	60	68	74	78	-
28	18	16	18	20	70	60	70	80	68	58	70	78	53	60	72	76	66	58	70	76	67	58	74	78	PALPITATIONS
29	18	18	20	22	70	70	80	80	55	68	78	80	62	68	77	78	68	67	74	78	67	69	76	78	HEADACHE
30	20	18	20	20	70	60	70	70	68	58	68	72	50	56	70	72	66	56	70	72	68	60	72	74	INSOMNIA

DERIPHYLLINE GROUP

Efficacy and safety

S.NO.	ACT SCORE				SUBJECTIVE RATING				FVC % PREDECTED				FEV 1				PEFR				FEV 1/FVC				ADRS
	0	1	2	3	0	1	2	3	0	1	2	3	0	1	2	3	0	1	2	3	0	1	2	3	
31	16	18	20	20	60	70	70	80	55	68	74	76	60	68	72	75	60	67	72	76	61	69	70	74	NAUREA
32	18	18	20	22	70	70	80	80	64	72	74	76	52	74	76	80	68	70	76	78	70	71	78	79	HEADACHE
33	18	18	16	20	70	70	60	80	68	70	58	78	66	68	60	79	67	70	61	78	69	72	60	80	VOMITING
34	18	18	20	20	70	70	80	80	55	68	74	78	67	66	74	76	65	67	74	76	65	67	76	79	NAUREA
35	16	17	20	19	50	50	70	60	76	81	83	82	51	70	75	80	57	66	68	74	60	65	72	80	NAUREA
36	17	17	20	21	50	50	70	75	75	82	82	85	58	64	68	77	59	71	78	82	62	68	70	72	EPIGASTRIC DISCOMFORT
37	16	16	20	21	50	50	70	75	78	80	81	873	63	62	77	79	65	68	71	75	58	63	75	79	-
38	18	18	19	20	60	60	60	70	54	83	84	84	60	60	74	75	61	71	75	78	70	72	78	76	TREMOR
39	16	17	20	20	50	50	70	70	66	82	83	82	61	65	69	76	56	68	68	72	65	68	70	74	-
40	19	20	20	21	60	70	70	70	75	79	80	80	64	62	75	79	57	73	76	80	59	63	73	75	NAUREA
41	16	16	17	18	50	50	50	60	61	80	80	80	58	60	71	80	56	66	68	76	58	62	71	72	-
42	20	20	18	20	70	70	60	65	55	81	82	81	64	67	70	79	58	75	68	74	62	68	76	79	HEADACHE
43	17	18	18	22	50	60	60	75	65	82	84	84	61	69	75	77	59	66	69	76	69	72	73	80	GIDDINESS
44	16	20	22	22	50	65	75	70	55	79	80	80	63	63	77	80	65	69	71	81	65	68	74	75	PALPITATIONS
45	17	18	20	20	50	60	65	65	60	80	81	83	59	65	72	78	58	68	70	74	70	72	76	78	TREMOR
46	19	18	22	20	60	60	75	65	60	83	84	84	66	70	73	75	61	75	71	78	58	63	75	79	-
47	16	16	18	20	50	50	60	65	65	81	83	81	61	62	79	78	67	71	74	75	59	62	71	73	NAUREA
48	21	17	20	22	75	50	70	80	57	80	80	83	64	72	69	76	62	69	69	77	62	65	78	80	EPIGASTRIC DISCOMFORT
49	20	20	22	22	70	75	80	80	65	82	83	82	63	65	70	79	57	66	67	72	60	68	75	78	TREMOR
50	17	17	21	21	50	50	70	75	60	79	80	80	58	72	73	74	65	73	76	78	65	69	72	73	-
51	17	19	20	22	50	60	70	70	76	82	84	85	61	64	70	80	58	75	69	76	62	68	76	81	PALPITATIONS
52	16	18	18	20	50	60	60	70	55	80	80	80	64	74	75	75	56	69	77	82	69	72	73	75	HEADACHE
53	18	20	20	22	60	65	65	80	60	81	82	83	59	65	68	74	61	68	70	75	58	62	71	72	-
54	16	20	20	22	50	65	65	70	55	79	80	80	63	70	73	77	65	71	74	81	65	69	77	79	HEADACHE
55	17	18	18	20	50	60	60	70	50	82	81	84	60	69	75	80	569	75	76	78	60	65	75	78	NAUREA
56	18	20	22	21	60	65	75	75	65	79	80	80	58	72	71	78	61	71	70	74	59	66	76	79	INSOMNIA
57	17	19	20	20	50	60	70	70	55	80	81	82	61	74	76	76	58	68	71	76	58	68	72	74	VOMITING
58	17	19	21	21	50	60	70	70	81	79	80	80	65	65	72	74	67	73	69	75	62	65	70	76	-
59	16	20	22	22	50	65	60	70	82	83	84	85	58	74	69	80	65	71	76	77	65	68	73	75	HEADACHE
60	16	20	18	20	50	65	60	70	76	81	83	84	52	65	75	75	66	75	70	81	60	63	71	73	PALPITATIONS

DERIPHYLLINE GROUP

Efficacy and safety

S.NO.	ACT SCORE				SUBJECTIVE RATING				FVC % PREDECTED				FEV 1				PEFR				FEV 1/FVC				ADRS
	0	1	2	3	0	1	2	3	0	1	2	3	0	1	2	3	0	1	2	3	0	1	2	3	
61	16	17	20	20	50	50	60	70	69	82	82	81	61	72	77	78	57	66	74	78	65	69	76	79	NAUREA
62	16	18	21	22	50	60	70	80	66	80	81	83	59	69	78	79	65	76	77	77	62	65	78	80	-
63	18	18	18	20	60	60	60	65	65	81	82	80	64	70	73	80	64	76	70	75	70	72	72	76	GIDDINESS
64	16	17	18	20	50	50	60	65	50	82	83	82	61	72	74	77	68	68	69	74	65	68	74	76	EPIGASTRIC DISCOMFORT
65	18	20	20	22	60	65	65	70	81	80	81	85	66	67	71	75	67	73	71	76	58	68	75	78	-
66	18	18	20	21	60	60	65	70	55	79	80	80	58	74	78	80	66	71	77	82	70	72	76	79	TREMOR
67	21	20	18	21	70	65	60	70	76	783	84	85	64	69	72	76	61	73	76	81	60	62	70	76	NAUREA
68	19	17	20	21	60	50	65	70	56	81	84	85	59	65	71	77	59	66	74	75	58	68	78	81	-
69	16	18	19	21	60	70	70	75	60	64	74	76	61	64	73	80	63	68	70	74	64	70	76	80	-
70	16	18	18	20	50	50	60	70	60	70	79	79	58	63	71	76	60	68	74	80	62	68	77	79	NAUREA
71	14	15	18	20	50	50	65	80	61	65	70	77	55	62	68	79	59	67	72	79	60	66	72	78	-
72	18	16	20	21	60	75	70	75	58	62	77	79	63	65	70	77	56	62	70	78	58	62	74	76	TREMOR
73	17	19	20	22	60	70	70	80	67	71	80	80	67	69	77	85	57	63	72	79	58	64	74	77	-
74	18	20	20	21	50	50	60	70	62	66	72	76	65	65	73	74	59	65	74	78	60	65	75	80	-
75	18	20	21	21	50	50	65	75	50	70	75	78	63	61	72	76	61	64	73	75	60	67	76	80	PALPITATIONS
76	16	19	19	20	50	60	70	80	59	62	73	75	58	66	69	78	60	66	71	76	60	68	78	80	-
77	17	18	18	20	50	65	70	75	60	64	70	78	65	68	72	79	58	67	72	74	58	63	70	76	-
78	18	18	21	22	60	70	70	75	59	70	80	80	52	70	74	77	63	65	69	79	60	67	74	79	PALPITATIONS
79	14	16	18	18	50	70	70	80	60	67	78	79	61	67	73	78	60	64	68	80	62	70	75	79	EPIGASTRIC DISCOMFORT
80	16	18	18	20	60	75	70	70	61	63	76	78	51	70	76	80	58	62	70	81	58	64	76	80	-

ACT- Asthma control test
FVC-Force vital capacity
FEV1- Forced expiratory volume in one sec
PEFR-Peak expiratory flow rate
ADRS- Adverse drug reactions

DERIPHYLLINE GROUP

Cost effectiveness

S.NO.	DISTANCE FROM HEALTH FACILITY	LOSS OF WAGES		TRAVEL		FOOD		TOTAL ID	INV	DIRECT COSTS		TMT OF ADR	GRAND TOTAL
		PT	ACP	PT	ACP	PT	ACP			TMT	TOTAL		
1	12	-	NIL	20	-	20	-	40		27.36		-	67.36
2	15	200	-	60	-	20	-	280		27.36		4.72	312.08
3	12	-	-	20	-	20	-	40		27.36		-	67.36
4	24	50	-	75	-	50	-	175		27.36		-	202.36
5	6	-	-	20	-	20	-	40		27.36		12.13	79.49
6	7	100	-	20	-	20	-	140		27.36		14.7	182.06
7	30	100	-	80	-	100	-	280		27.36		-	307.36
8	14	-	-	40	-	20	-	60		27.36		2.95	90.31
9	7	-	-	20	-	20	-	40		27.36		4.72	72.08
10	6	50	-	20	-	20	-	90		27.36		14.7	132.06
11	15	-	-	60	-	50	-	110		27.36		-	137.36
12	20	-	-	60	-	50	-	110		27.36		2.95	140.31
13	40	150	YES	100	100	100	100	550		27.36		-	577.36
14	10	70	-	20	-	20	-	110		27.36		-	137.36
15	15	50	-	60	-	50	-	160		27.36		4.72	192.08
16	14	-	-	50	-	20	-	70		27.36		14.7	112.06
17	18	-	-	70	-	40	-	110		27.36		-	137.36
18	13	100	-	60	-	50	-	210		27.36		2.95	240.31
19	8	-	-	40	-	20	-	60		27.36		-	87.36
20	12	-	-	60	-	20	-	80		27.36		4.72	112.08
21	3	50	-	20	-	20	-	90		27.36		-	117.36
22	8	-	-	20	-	20	-	40		27.36		12.13	79.49
23	14	100	-	100	-	50	-	250		27.36		14.7	292.06
24	12	500	-	40	-	50	-	590		27.36		-	617.36
25	12	500	-	50	-	50	-	600		27.36		-	627.36
26	10	-	-	20	-	20	-	40		27.36		-	67.36
27	3	200	-	20	-	-	-	220		27.36		-	247.36
28	15	200	-	50	-	20	-	270		27.36		-	297.36
29	2	100	-	20	-	-	-	120		27.36		4.72	152.08
30	1	100	-	-	-	-	-	100		27.36		-	127.36

DERIPHYLLINE GROUP

Cost effectiveness

S.NO	DISTANCE FROM HEALTH FACILITY	LOSS OF WAGES		TRAVEL		FOOD		TOTAL ID	INV	DIRECT COSTS		TMT OF ADR	GRAND TOTAL
		PT	ACP	PT	ACP	PT	ACP			TMT	TOTAL		
31	10	500	-	40	-	20	-	560		27.36		14.7	602.06
32	6	100	-	40	-	20	-	160		27.36		4.72	192.08
33	7	300	-	40	-	20	-	360		27.36		15.8	403.16
34	15	100	-	60	-	20	-	180		27.36		14.7	222.06
35	19	-	-	60	-	70	-	130		27.36		14.7	172.06
36	2	200	-	20	-	20	-	240		27.36		2.95	270.31
37	10	200	-	40	-	30	-	270		27.36		-	297.36
38	13	100	-	40	-	30	-	170		27.36		-	197.36
39	5	-	-	20	-	20	-	40		27.36		-	67.36
40	15	200	-	60	-	70	-	330		27.36		14.7	372.06
41	4	100	-	20	-	20	-	140		27.36		-	167.36
42	14	200	-	40	-	30	-	270		27.36		4.72	302.08
43	5	-	-	20	-	20	-	40		27.36		-	67.36
44	17	50	-	60	-	70	-	180		27.36		-	207.36
45	11	100	-	40	-	30	-	170		27.36		-	197.36
46	16	100	-	60	-	70	-	230		27.36		-	257.36
47	15	-	500	60	60	70	70	760		27.36		14.7	802.06
48	6	200	-	30	-	20	-	250		27.36		2.95	280.31
49	9	100	-	30	-	20	-	150		27.36		-	177.36
50	16	500	-	60	-	70	-	630		27.36		-	657.36
51	20	-	400	70	70	100	100	640		27.36		-	667.36
52	3	70	-	20	-	20	-	110		27.36		4.72	142.08
53	17	100	-	60	-	70	-	230		27.36		-	257.36
54	8	150	-	30	-	20	-	200		27.36		4.72	232.08
55	5	70	-	20	-	20	-	110		27.36		14.7	152.06
56	12	200	-	40	-	30	-	270		27.36		-	297.36
57	20	-	-	70	-	100	-	170		27.36		15.08	212.44
58	20	100	-	70	-	100	-	270		27.36		-	297.36
59	17	100	-	60	-	70	-	130		27.36		4.72	162.08
60	5	-	-	20	-	20	-	40		27.36		-	67.36

DERIPHYLLINE GROUP

Cost effectiveness

S.NO	DISTANCE FROM HEALTH FACILITY	LOSS OF WAGES		TRAVEL		FOOD		TOTAL ID	INV	DIRECT COSTS		TMT OF ADR	GRAND TOTAL
		PT	ACP	PT	ACP	PT	ACP			TMT	TOTAL		
61	11	-	300	40	40	30	30	440		27.36		14.7	482.06
62	7	50	-	30	-	20	-	100		27.36		-	127.36
63	3	250	-	20	-	20	-	290		27.36		-	317.36
64	14	200	-	40	-	30	-	270		27.36		4.62	301.98
65	18	250	-	60	-	70	-	380		27.36		-	407.36
66	15	100	-	60	-	70	-	230		27.36		-	257.36
67	4	-	-	20	-	20	-	40		27.36		14.7	82.06
68	10	100	-	40	-	30	-	170		27.36		-	197.36
69	20	100		70		100		290		27.36		-	317.36
70	10	150		40		40		230		27.36		12.13	269.49
71	6	-	200	30	30	20	20	300		27.36		-	327.36
72	1	-	100	20	20	20	20	180		27.36		-	207.36
73	8	-		30		20		50		27.36		-	77.36
74	19	200		60		70		330		27.36		-	357.36
75	5	-	300	20	20	20	20	380		27.36		-	407.36
76	7	100		30		20		150		27.36		-	177.36
77	4	200		20		20		240		27.36		-	267.36
78	12	150		40		30		220		27.36		-	247.36
79	17	300		60		70		430		27.36		-	460.31
80	19	150		60		70		280		27.36		-	307.36

PT-pationt
ACP-accompaning person
ID-indirect cost
TMT-treatment
ADR-adverse drug reaction
ECG-electro cardio graphy
CXR-chest ex-ray
HB-hemoclobin
TC-total count
RBS-random blood sugar
BT-bleading time
CT-clotting time

DERIPHYLLINE GROUP

Investigations

S. NO	ECG		CXR		HB %		TC		RBS		SERUM CREATININE		BL UREA		SGOT		SGPT		BT		CT	
	0	**3**	**0**	**3**	**0**	**3**	**0**	**3**	**0**	**3**	**0**	**3**	**0**	**3**	**0**	**3**	**0**	**3**	**0**	**3**	**0**	**3**
1	N	N	N	N	10.1	10.2	8421	7804	120	110	0.8	0.9	1.4	14.6	23.6	24	22	20	5	4.9	6	6.2
2	N	N	N	N	11.2	11.3	8620	7610	130	120	0.9	0.7	1.45	13.9	23.8	26	20	21	5.2	5.1	5.6	5.6
3	N	N	N	N	10.6	10.8	7410	7816	116	118	0.8	0.9	12.2	12.8	23.6	24.2	19	20	5.1	5	5.6	6
4	N	N	N	N	11.3	11	6410	7602	124	126	0.9	1	13.2	14	25.1	25.6	20	22	5.3	5.2	6.1	6.2
5	N	N	N	N	10	10.2	8141	6234	132	134	0.9	0.8	13.6	13.4	24.2	24.8	19	20	5.2	5.1	6.1	5.6
6	N	N	N	N	9.4	9.6	8940	7016	130	120	0.8	0.9	13.4	13.6	22	23.4	20	21	5.4	5.3	6	5.4
7	N	N	N	N	11	11.2	8412	8623	110	120	0.7	0.7	12.8	12.9	24	23.6	19	23	5.3	5.2	6.2	6.3
8	N	N	N	N	9.6	9.4	5162	7201	130	120	0.8	0.8	12.9	13.2	23	24.2	18	19	5	4.9	5.6	5.4
9	N	N	N	N	11	11	6238	6381	116	141	0.9	1	13.8	14.4	23.4	25.2	19	21	5.2	5.1	6.2	5.4
10	N	N	N	N	9.8	9.6	7162	7816	120	121	0.78	0.9	13.4	14	23.6	24.4	22	23	5	4.9	6.3	6
11	N	N	N	N	10.2	10.4	6841	7620	110	116	0.8	0.8	14	13.2	24.2	25.2	20	22	5.1	5	5.4	6.2
12	N	N	N	N	9.6	9.8	7810	7600	113	118	0.7	0.9	12.2	12.8	25.1	25	21	23	5.4	5.3	6	5.6
13	N	N	HYPER VENTILATION	HYPER VENTILATION	11.2	11	7160	8100	114	125	0.8	0.7	13.4	13.6	23.7	24.5	23	24	5.3	5.2	6.2	6.1
14	N	N	N	N	8.6	8.8	8600	9000	126	100	0.8	0.9	14.4	12.9	23	23.4	19	21	5.3	5.2	5.6	5.4
15	N	N	N	N	9.2	9.4	8916	6780	104	115	0.9	1	13	13.7	22.6	23.6	18	20	5	4.9	6.1	6
16	N	N	N	N	8.8	9	7416	7818	114	127	0.7	0.9	12.8	14.1	23.2	24.2	20	22	5.2	5.1	1	6.2
17	N	N	N	N	10.1	10	7618	7114	116	120	0.9	0.8	13.6	13.8	24.4	25.1	19	20	5.1	5	5.4	5.6
18	N	N	N	N	10.4	10.2	8617	7918	128	110	0.9	0.8	12.9	15	23.4	24.3	20	21	5	4.9	6	6.1
19	N	N	N	N	10	9.8	7148	7618	109	117	0.8	0.9	13.7	14.4	23.6	24.6	22	23	5.4	5.3	6.2	5.4
20	N	N	N	N	9.6	9.8	7418	7614	110	120	0.8	0.7	12.9	14.2	24.2	24.6	18	19	5.3	5.2	6.1	5.4
21	N	N	N	N	9.8	10	8410	7914	120	116	0.8	0.8	14	14.2	25.2	23.6	20	18	5	4.9	5.6	6.3
22	N	N	N	N	8.8	8.6	8619	8810	118	132	0.9	0.1	14.4	13	22.9	23.4	20	22	5.2	5.1	5.4	6
23	N	N	N	N	10.1	10.2	7816	7610	130	121	0.7	0.8	12.6	12.8	22.8	23.6	22	24	5	4.9	6.3	6.2
24	N	N	N	N	9.6	9.8	8810	8901	108	119	0.8	0.9	12.8	13.6	23.6	24.2	20	23	5.2	5.1	6.3	6.1
25	N	N	N	N	10.2	10	8671	7819	116	131	1	0.8	14.1	12.9	24.9	25.2	21	22	5.1	5	6	5.4
26	N	N	N	N	11	11	7610	6901	120	107	0.9	0.8	13.4	13.7	23.4	24	23	21	5.4	5.3	6.2	5.4
27	N	S..TACHYCARDIA	HYPER VENTILATION	HYPER VENTILATION	11.2	12	9700	9000	130	114	0.7	0.9	12.8	14.6	23.6	24.2	19	21	5	4.9	6.1	5.4
28	N	N	N	N	10.6	11	7900	9301	113	120	0.8	0.7	13.6	14.7	24.2	22.8	20	21	5.2	5.1	6.3	6
29	N	N	N	N	10.8	11	8610	8510	114	121	0.8	0.8	13.9	14.1	25	23.4	23	22	5.4	5.3	6.3	6.2
30	N	N	N	N	9.6	9.4	6714	7612	115	129	0.9	0.8	14.2	13	22.8	23.6	19	20	5.4	5.3	5.4	6.1

DERIPHYLLINE GROUP

Investigations

S. NO	ECG		CXR		HB %		TC		RBS		SERUM CREATININE		BL UREA		SGOT		SGPT		BT		CT	
	0	3	0	3	0	3	0	3	0	3	0	3	0	3	0	3	0	3	0	3	0	3
31	N	N	N	N	10.6	10.4	6718	7160	122	106	0.7	0.7	13.7	12.8	23.8	24.2	20	21	5.2	5.1	6	
32	N	N	N	N	10.2	10.4	8601	8701	128	123	0.7	0.8	12.9	13.6	23.4	23.8	20	21	5.1	5	6.2	
33	N	N	N	N	10.1	10	8174	8410	112	127	0.9	0.9	14	13.6	24.2	25	21	23	5	4.9	6.1	
34	N	N	N	N	9.6	9.8	7612	8610	124	126	0.8	0.9	12.8	13	23.6	24	22	20	5	4.9	6.2	
35	N	N	N	N	10.2	10.6	9620	9612	120	110	0.8	0.9	14.2	14.6	23.2	24.1	21	20	5	4.9	6.1	
36	N	N	N	N	9.6	9.8	7420	6986	119	117	0.7	1.1	12.2	13.5	22	25.2	18	20	5.3	5.2	5.4	
37	N	N	N	N	10.1	11.6	8724	9426	112	127	0.9	1	12.5	13.7	23.6	26	19	21	5	4.9	6	
38	N	N	N	N	10.2	11.2	8626	7852	124	116	0.7	0.9	12.2	13.9	24.2	25.6	19	19	5	4.9	5.6	
39	N	N	N	N	8.6	8.8	8567	9784	121	127	0.9	1	12.5	13.7	22.8	24.3	20	22	5.1	5	5.6	
40	N	N	HYPER VENTILATION	HYPER VENTILATION	11.2	9.6	9486	9674	117	116	0.7	0.8	12.8	13.2	23.4	23.6	22	21	5.1	5	6	
41	N	N	N	N	11	10.1	9847	9658	127	119	0.9	0.9	13.5	13.7	24.2	24.2	22	20	5.1	5	5.6	
42	N	N	N	N	10.1	11.2	8859	8721	118	127	0.8	1.1	12.8	13.2	23.8	23.2	19	20	5	4.9	5.4	
43	N	N	N	N	9.6	10.2	8841	8970	127	121	1.0	0.9	12.5	13.5	22	24.1	19	18	5	4.9	5.6	
44	N	N	N	N	10.2	10.1	9216	6920	119	112	0.8	0.9	12.2	13.2	23.6	25.2	21	20	5	4.9	5.4	
45	N	N	N	N	8.8	11.2	9784	8741	127	124	0.9	1	13.5	13.7	22.6	25.6	19	23	4.6	4.5	5.6	
46	N	N	N	N	10.3	12	6129	7840	127	121	0.7	0.9	13.9	14.2	23.8	22.8	22	22	5.1	5	6	
47	N	N	N	N	8.6	10	8641	8649	120	117	0.7	0.9	12.2	12.8	23.9	24.9	21	23	5.1	5	5.4	
48	N	N	N	N	10.1	11.2	6947	9920	112	119	0.8	0.9	13.5	14.2	24	25.6	18	19	5.2	5.1	6	
49	N	N	N	N	8.6	8.8	7469	8497	124	127	0.7	0.8	13.5	14.1	23.6	26	21	20	5.1	5	5.6	
50	N	N	N	N	10	9.6	7849	8421	121	118	0.7	0.9	12.8	13.2	23.2	24.6	21	23	4.9	4.8	6	
51	N	S..TACHYCARDIA	N	N	10.1	10.2	9290	6482	117	119	0.9	1.1	12.5	13.5	23.6	24.1	20	22	5	4.9	5.4	
52	N	N	N	N	8.9	9.2	9762	8217	127	116	0.8	1	14.2	13.9	23.5	25.6	18	19	5.2	5.1	5.5	
53	N	N	N	N	9.7	11.2	7614	6148	115	127	0.8	0.9	12.2	12.8	23.6	25.2	20	21	5	4.9	6	
54	N	N	N	N	9	8.8	8810	7482	117	118	0.9	1.1	12.8	13.2	22	25	19	23	5	4.9	5.6	
55	N	N	N	N	9.6	10	8470	7621	119	120	1.0	0.8	15.5	14.1	23.9	25.6	21	22	5.3	5.2	5.5	
56	N	N	N	N	10.2	11.2	9847	9421	127	112	0.7	0.9	12.2	12.8	23.8	24.8	21	23	5.1	5	5.4	
57	N	N	N	N		10.1	9486	8641	118	124	0.9	1.1	12.5	13.7	21.6	23.2	22	18	5	4.9	5.6	
58	N	N	N	N	8.8	10	7841	8490	117	121	0.8	0.9	12.8	13.2	23.6	24.1	20	19	5.1	5	5.4	
59	N	N	N	N	8.6	9.7	9714	9947	127	119	0.9	1	13.9	14.3	23.8	25.2	21	20	4.9	4.8	5.4	
60	N	N	HYPER VENTILATION	HYPER VENTILATION	10.4	10.1	8914	8610	118	127	1.1	1.1	12.2	13.9	22	25.6	21	23	5.1	5	5.5	

DERIPHYLLINE GROUP

Investigations

S. NO	ECG		CXR		HB %		TC		RBS		SERUM CREATININE		BL UREA		SGOT		SGPT		BT		CT	
	0	3	0	3	0	3	0	3	0	3	0	3	0	3	0	3	0	3	0	3	0	3
61	N	N	N	N	9.7	9.6	8771	7620	120	118	0.9	0.8	12.2	12.8	24.2	25.2	20	22	4.6	4.5	5.6	6.2
62	N	N	N	N	10	10.2	9619	7612	112	119	0.7	0.9	12.5	13.8	23.6	25.6	18	23	5.1	5	6	6.2
63	N	N	N	N	11.2	11.4	8912	9753	124	127	1.1	1	12.5	13.7	23.2	24.6	19	23	5.1	5	5.6	6.1
64	N	N	N	N	8.6	8.8	7810	8442	121	117	0.7	0.9	14.4	13.9	23.6	24.1	20	18	5	4.9	5.5	6.2
65	N	N	N	N	11.2	11.6	9846	8898	124	120	0.8	0.9	13.5	12.8	23.6	25.2	22	21	5.2	5.1	6	6.3
66	N	N	N	N	10.2	11.2	8818	9614	119	112	0.9	0.9	13.9	14.6	22.8	24.6	18	20	5.4	5.3	5.6	6.1
67	N	N	N	N	9.6	8.8	9626	7941	117	124	0.9	1	14.2	14.2	24.6	24.1	19	21	5	4.9	5.6	6
68	N	N	N	N	10.1	11.1	8421	8561	128	120	0.7	0.8	12.6	13.7	22	25.2	21	23	5.1	5	6.1	6.3
69	N	N	N	N	8.6	10.6	8411	7128	125	130	0.9	1.1	12.4	13.4	23.6	22.8	20.6	20	5	4.9	5.4	5.6
70	N	N	N	N	10.6	9.8	8617	9759	135	126	1.0	0.9	12.5	13.7	23.3	23.6	20.3	21.1	5.2	5.1	5.8	5.4
71	N	N	N	N	10.4	12.4	8754	9688	129	117	0.8	1	12.6	13.6	23.1	23.8	20.1	19	5	4.9	6	6.2
72	N	N	N	N	11.6	10.8	9771	8712	123	134	0.8	1	13	14.1	23.8	23.3	20.8	20	5.1	5	5.6	6.1
73	N	N	N	N	12	8.8	8744	8941	118	124	0.9	1.1	12.9	14.3	23.3	23.7	20.3	18	5.3	5.2	6.2	6
74	N	S.TACHYCARDIA	N	N	9.4	11	8676	9781	133	125	0.8	0.9	13.5	12.6	22.9	23.6	20.9	21	5	4.9	5.6	6.3
75	N	N	N	N	11.4	10.2	9942	8418	127	122	0.8	0.9	13.1	13.8	22.8	23.3	20.8	22	5.1	5	5.4	6
76	N	N	HYPER VENTILATION	HYPER VENTILATION	8.9	10.4	8641	8917	119	131	1.0	1.1	13.2	14	23.1	23.5	20.1	20	5.3	5.2	6	0.8
77	N	N	N	N	11.2	12.4	8110	9361	136	121	1.1	1.2	13.1	14.2	23.6	24.2	20.6	19	5.2	5.1	5.6	6.3
78	N	N	N	N	10.6	9.1	8916	8810	126	132	0.9	1	12.8	13.8	23.3	21	20.3	18	5.3	5.2	5.6	6
79	N	N	N	N	10.8	10.2	9612	7104	113	128	1.0	1	12.6	13.4	23.4	24	20.4	20	5.2	5.1	6	6.3
80	N	N	N	N	9.6	9.8	7745	8628	121	140	0.8	1	12.4	13	24	23.1	20	22	5	4.9	5.8	6.2

INSTITUTIONAL ETHICS COMMITTEE

CHENGALPATTU MEDICAL COLLEGE , CHENGALPATTU

APPROVAL OF ETHICAL COMMITTEE

To

Dr.M.Nandhini Priya,
MD Pharmacology,
(2nd Year)
Chengalpattu Medical College,
Chengalpattu.

Dear Dr.

The Institutional Ethical Committee of Chengalpattu Medical College reviewed and discussed your application to conduct the clinical / dissertation work entitled

"EFFICACY,SAFETY AND COST EFFECTIVENESS OF ORAL DOXOFYLLINE AND THEOPHYLLINE FOR MILD TO MODERATE PERSISTENT BRONCHIAL ASTHMA: A RANDOMIZED PROSPECTIVE OPEN LABELED COMPARATIVE STUDY".

ON 11.06.2014

The following documents reviewed

1. Trial protocol, dated _____version no
2. Patient information sheet and informed consent form in English and / or
   vernacular language.
3. Investigators Brochure, dated _____version
4. Principal Investigators current CV
5. Investigators undertaking

The following members of the Ethics committee were present at the meeting held on

Date 11.06.2014 Time 11.30 Noon Place Chengalpattu Medical College

Approved Jamuna Rani Chairman Ethics Committee

11/6/14 Member secretary of Ethics Committee.

Name of each member with designation:-

Clinical Members

1. Dr.R.Muthuselvan MD.,
   Prof & HOD of Medicine, CHMC

2. Dr.C.Srinivasan MD.,
   Prof & HOD of Surgery, CHMC

Biological Scientist

3. Dr.K.Baskaran MD.,
   Asso Prof of Pharmacology, CHMC

Non Clinical Member

4. Dr.P.Parasakthi MD
   Prof & HOD of Forensic Medicine,CHMC

5. Member from Nongovernmental
   Voluntary Organisation : Mr.P.Durairaj

6. Philosopher : Mr.K.S.Ramprasad

7. Lawyer : Lr. I. M. Karimala Basha

8. Layperson : Mr.Dilli

We approve the clinical trial to be conducted in its presented form

The Institutional Ethics Committee expects to be informed about the progress of the study and any SAE occurring in the course of the study, any changes in protocol and patient information / informed consent and asks to provide copy of final report.

Yours sincerely

11/6/14

Member secretary, Ethics Committee