COMPARATIVE STUDY OF RACEMIC SALBUTAMOL AND LEVOSALBUTAMOL IN PATIENTS WITH BRONCHIAL ASTHMA

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CHENNAI – TAMILNADU

INSTITUTE OF PHARMACOLOGY
MADURAI MEDICAL COLLEGE AND GOVERNMENT RAJAJI HOSPITAL, MADURAI

CERTIFICATE

This is to certify that the dissertation entitled **"COMPARATIVE STUDY OF RACEMIC SALBUTAMOL AND LEVOSALBUTAMOL IN PATIENTS WITH BRONCHIAL ASTHMA"** is a bonafide record of work done by **Dr. K. Raadhika,** under my guidance and supervision in the Institute of Pharmacology, Madurai Medical College, Madurai during the period of her Postgraduate study for **M.D. Pharmacology** from 2004 - 2007.

Place: Madurai
Date:

Director and Professor
Institute of Pharmacology,
Madurai Medical College,
Madurai.

DECLARATION

I, **Dr. K. RAADHIKA** Solemnly declare that the dissertation titled **"COMPARATIVE STUDY OF RACEMIC SALBUTAMOL AND LEVOSALBUTAMOL IN PATIENTS WITH BRONCHIAL ASTHMA"** has been prepared by me under the able guidance and supervision of **Dr.N.MEENAKSHIAMMAL, M.D.,** Former Director and Professor of Pharmacology, Institute of Pharmacology, Madurai Medical College, Madurai in partial fulfilment of the regulation for the award of M.D., (PHARMACOLOGY) degree examination of The Tamil Nadu Dr. M.G.R. Medical University, Chennai to be held in March 2007.

This work has not formed the basis for the award of any degree or diploma to me, previously from any other university to any one.

Place: Madurai
Date:

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"No academic endeavor is single handedly accomplished.

This work is no exception"

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CONTENTS

ABBREVIATIONS

AIDS	-	ACQUIRED IMMUNO DEFICIENCY SYNDROME
COPD	-	CHRONIC OBSTRUCTIVE PULMONARY DISEASES
ER	-	ENDOPLASMIC RETICULAM
FDA	-	FOOD AND DRUG ADMINISTRATION
FEV_1	-	FORCE EXPIRATORY VOLUME
FVC	-	FORCE VITAL CAPACITY
GDP	-	GUANOSINE 5' DIPHOSPHATE
GERD	-	GASTRO EOSOPHAGIAL REFLUX DI
GINA	-	GLOBAL INITIATIVE FOR ASTHMA
HIV	-	HUMAN IMMUNO DEFICIENCY VIRUS
ICD	-	INTERNATIONAL CODE FOR DISEASES
IP_3	-	INOSITOL 1, 4,5 TRI PHOSPHATE
IUTALD	-	INTERNATIONAL UNION AGAINST TUBERCULOSIS AND LUNG DISEASE
LFT	-	LIVER FUNCTION TEST
MDI	-	METERED DOSE INHALER
NAEPP	-	NATIONAL ASTHMA EDUCATION AND PREVENTION PROGRAMME
NSAIDS	-	NON STEROIDAL ANTIINFLAMMATORY DRUGS

PAF	-	PLATELET ACTIVATING FACTOR
PEFM	-	PEAK EXPIRATORY FLOW METER
PEFR	-	PEAK EXPIRATORY FLOW RATE
PIP_2	-	PHOSPHATIDYLINOSITOL 4,5 – BIPHOSPHATE
RFT	-	RENAL FUNCTION TEST
TB	-	TUBERCULOSIS
WHO	-	WORLD HEALTH ORGANISATION

INTRODUCTION

"He who really understands what is involved in the breathing of man, has already sensed the breath of God"[1].

Asthma is a serious global health problem, affects people of all ages, in all parts of the world. Despite greatly increasing knowledge of the immuno pathological processes, characteristics of the disease and apparent improvements in treatment, morbidity is increasing rather than decreasing.

There is now great potential for improving the management of asthmatic patients by encouraging more rational use of treatments already in existence. The Global initiative for Asthma (GINA) was implemented to develop a network of individuals, organizations, and public health officials to disseminate information about the care of patients with asthma while at the same time assuring a mechanism to incorporate the result of scientific investigations into asthma care[2].

A greater number of clinicians are now aware of these management recommendations. A world wide unified approach to the management of

asthma would be ideal. But this approach is not feasible because of inter country socioeconomic variables and the financial burden of therapy, which will be too heavy for some of the resource poor settings.

There are similarities in the treatment of asthma and diabetes, since in both diseases the aim is to allow the patient to be as independent as possible and to make treatment changes as appropriate to maintain clinical control. However, patients should get professional advice whenever self-management has not been successful. Moreover, patients contact their health care professionals for review and advice periodically (or) as and when required.

The principles of management in general are to

- Recognize asthma,
- Abolish Symptoms,
- Restore normal (or) best possible long term airway function,
- Reduce the risk of severe attacks,
- Enable normal growth to occur in children, and
- Minimize absence from school (or) work.

The other aspects to be considered in the management are

- Patient and family participation,
- Avoidance of identified causes where ever possible, and
- Use of lowest effective doses of convenient medications minimizing short-term and long-term side effects[3].

In general, allow all the patients to lead good quality of life without symptoms, free from side effects of drugs, adjusted and modified by patient involvement.

Drug therapy for asthma includes those that **inhibit smooth muscle contraction** (beta adrenergic agonist, methyl xanthines, anticholinergics) and agents that **prevent (or) reverse inflammation** (glucocorticoids, mast cell stabilizers and leukotriene modifiers) [4].

Salbutamol, a short acting, selective beta-2 adrenoreceptor agonist is one of the most commonly used bronchodilators in the treatment of reversible airway obstruction[5]. Salbutamol is included in Essential drug list [6] (WHO List 22.5).

Salbutamol has been marketed as a racemic mixture, although beta-2 agonist activity resides almost exclusively in the (R)-enantiomer.[7] It is an active enantiomer of racemic salbatamol while the (S)-enantiomer is inactive and this may be associated with airway hyper reactivity and has more adverse effects.[8,9] Hence, research was focused to develop an enantiomerically pure (R)–salbutamol known as Levosalbutamol, which has been documented, as more efficacious and without potential unfavourable effect than racemic salbutamol in enhancing airflow of patients with bronchospasm. [10,11] Several drugs are now being marketed or being developed as single enantiomers in place of a previous racemic mixture, a process known as **chiral** '**Switching**' or **Racemic 'Switching'**[12,13]. Levosalbutamol is one such molecule. [14,15]

Published reports state that levosalbutamol a molecule approved in 2004 for regular use has better effect then racemic form. However, not much studies made on the usefulness of levosalbutamol from south India. Hence the present study is undertaken to assess the efficacy of levosalbutamol compared to racemic salbutamol in patients with bronchial asthma.

AIM OF THE STUDY

1. To compare the efficacy and tolerability of Racemic salbutamol and Levosalbutamol

2. To identify the side effects of each, and to recommend the appropriate one.

REVIEW OF LITERATURE

Etymology

Asthma is an ancient Greek word meaning “Panting (or) short drawn breath” which might has probably derived from the word ‘azo’. The word azo means breath hard. It was called as in middle English “asma” derived from medieval Latin, a modification of Greek asthma.

Bronchial asthma in Ayurveda[16]

In Ayurveda, and Indian system of medicine the disease is termed as “shwasa” in general and it has classified this disease into further five subtypes of which one is ‘Tamakashwasa’, which shows a great similarity in its symptomatology with bronchial asthma.

Bronchial asthma in Siddha [17]

In siddha , an ancient Tamil medicine, the disease Asthma is described as Iraippu Nooi ,Eluppu nooi ,suvasa kasam

In International Code for Diseases the Number for Asthma is given as (ICD-9CM CODES WHO 9th edition)

493.9- Asthma, unspecified

493.1- Intrinsic Asthma

493.0- Extrinsic Asthma

Definitions of Asthma [18,19]

Based on the functional consequences of airway inflammation, an operational description of asthma is that:

Asthma is a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role. The chronic inflammation causes an associated increase in airway hyper responsiveness that leads to recurrent episodes of wheezing, breathlessness, chest tightness, and coughing, particularly at night (or) in the early morning. These episodes are usually associated with widespread but variable airflow obstruction that is often reversible either spontaneously (or) with treatment.

Asthma is defined by the American thoracic society [124] as a disease characterized by an increased responsiveness of the trachea and bronchi to various stimuli manifested by a widespread narrowing of the airways that changes in severity either spontaneously (or) as a result of therapy.

Historical development of Adrenergic Agonists[20]

Airway regulation involves both the sympathetic (adrenergic) and parasympathetic (cholinergic) autonomic nervous system. In response to stress, allergic reactions (or) physical activity the neurotransmitters

norepinephrine and epinephrine are released. Epinephrine is a powerful bronchodilator and vasopressor. Many of the currently used adrenergic agonist bronchodilators are structurally related to epinephrine.

Ancient folk medicine 18^{th} century	-	Inhalation of smoke from the burning of variety of solanaceous plants including. Atropa belladonna (deadly night shade), Hyosyamus niger (black hen bane), Datura stramonium (Jimson weed, Jamestown weed (or) thorn apple)
1895	-	Extract of sheep adrenal gland Intravenously for Vasopressor effect reported by Oliver and Shafer. Abel-who named it epinephrine, Takamine - who called it adrenaline.
1904	-	Aldrich - identified the correct empirical formula for epinephrine $C_9H_{13}NO_3$ - and synthesised the compound independently
1910	-	The term sympathomimetics was introduced Barger and dale investigated the pharmacological activity of a number of synthetic amines structurally related to epinephrine.

Epinephrine	-	Derived from the Chinese herbal medicine Mahuang (Ephedra vulgaris) Employed for many years as a treatment for bronchial asthma first orally effective adrenergic bronchodilator
1924	-	Chen and Schmidt isolated the active substance and described the physiological effects
1930	-	Ephedrine as bronchodilator through the 1930.
1940	-	Substitution of methylgroup of epinephrine lead to ephedrine Konzett observed N- isoprophyl derivative of epinephrine (isoprenaline, isoproterenol)
1948	-	Ahlquist identified alpha & beta receptors.
1960s and 1970s	-	Large number of β_2 selective bronchodilators were developed during 1960s & 1970s. Allen and Hanburys developed a compound salbutamol by replacing the side chain of isoproterenol by tert-butyl group replacing Isopropyl group of Metaproterenol with tert-butyl group terbutaline is prepared
		Additional enlargement of the side- chain amino

		function of Metaproterenol, Fenoterol was prepared by Bochringer Ingelhein
To minimize vasodilatation and cardiac side effects additional drugs were investigated	-	Examples of compounds brought to various stages of development, including marketing approval are solterenol, salmefamol, carbuterol, denbuterol, rimiterol, mabuterol, pirbuterol, quinterenol, procaterol and broxaterol
Approaches to longer acting bronchodilators	-	Bitolterol, Bambuterol (Prodrug of terbutaline)
Newer aerosol drugs	-	Formoterol and Salmeterol

List of Drugs during 1994 – 2004			
S.No	**Date of Approval from FDA, (USA)**	**Name of the Drug**	**Pharmacological Classification**
215	16-07-2004	Levosalbutamol tablet 1mg/2mg & syrup 1mg/5ml	For obstructive diseases

Document type – New Drug Profile
Affiliations : 1: Adis International Limited, Auckland, New Zealand

ETIOLOGY [21,22]

Asthma cannot be cured, but could be controlled. The strongest risk factors for developing asthma are genetically susceptible host, allergens, respiratory infections, and certain occupational and environmental stimuli. Once the inflammation and bronchial hyper reactivity are present, can be triggered by additional factors, including exercise, inhalation of cold, dry air, cigarette smoke, physical (or) emotional stress, inhalation of irritants, pharmacological agents such as, NSAIDS and beta blockers, methacholine and histamine, respiratory infections (viral / bacterial),and allergens.

Allergens

a. Ingested (fish, nuts, strawberries)
b. Inhaled (Dust, Pollen, house dust mite)
c. Food additives (tartazine, ajinomoto)
d. Occupational allergens (grain dust, wood dust)

EPIDEMIOLOGY [23,24]

The prevalence of asthma is rising in most parts of the world. It is estimated that 4-5% of the population of United States is affected. Data from the centers for disease control and prevention suggest that 10 to 11 million persons had acute attacks in 1998. It has varied considerably within countries. It is more prevalent in developed countries than developing ones. In India,

prevalence of asthma has been found to be around 6% in the majority of surveys. However, it has been reported to vary from 2 to 17% in different study population. The disease can start at any age, but in a majority, it starts before 10 years of age. It is twice as common amongst boys than girls, where as in adults the Male-Female ratio is usually equal.

The scale of the problem in different developed countries are provided below: Table 1[25]

Between 100 and 150 million people around the globe, roughly the equivalent of the population of the Russian Federation, suffer from asthma and this number is rising. World-wide, deaths from this condition have reached over 180,000 annually.

TABLE 1: SCALE OF THE PROBLEM IN DIFFERENT COUNTRIES

Country	**Percentage of Asthma**
1. Swiss	8% (2%-25-30years)
2. US	60%(1980s)
3. Japan	7%(severe), 30% (moderate)
4. Caroline Islands	50%(children)
5. Brazil, Costa Rica, Panama, Peru, Uruguay	20-30%(children)
6. Kenya	20%
7. India	10-15%
8. Papua New Guinea	0%

The human and economic burden

Mortality due to asthma is not comparable in size to the day-to-day effects of the disease. Although largely avoidable, asthma tends to occur in epidemics and affects young people. The human and economic burden associated with this condition is severe. The costs of asthma to society could be reduced to a large extent through concerted international and national action.

World-wide, the economic costs associated with asthma are estimated to exceed those of TB and HIV/AIDS combined.

In the United States, for example, annual asthma care costs (direct and indirect) exceed US$6 billion.

At present Britain spends about US$1.8 billion on health care for asthma and because of days lost through illness.

In Australia, annual direct and indirect medical costs associated with asthma reach almost US$460 million.

PATHOPHYSIOLOGY [18,26,27]

Gross appearance

Patients dying from acute episodes of asthma have bulky over distended lungs which fail to deflate when chest is opened. The airways are thickened and plugged with secretions.

Microscopic appearance

The main feature of asthmatic airways are marked thickening of basement membrane, bronchial smooth muscle hypertrophy and damaged epithelium, much of which is shed. The bronchial wall contains the inflammatory cells, frequent and characteristic being eosinophils. Other cells include neutrophilis, lymphocytes, mast cells and plasma cells. The mucus or bronchial secretions of an asthmatic patient contains eosinophils, desquamated airway epithelial cells termed creola bodies, charcot leydon crystals and thick thread like sputum called curshman's spirals.

IMMUNOLOGICAL ASPECTS OF ASTHMA [28,29]

Early phase reaction

Antigen absorption occurs from the mucus membrane, gut, respiratory tract or skin. These antigens combine with human proteins and this foreign protein or complex comes into contact with macrophages on the mucosal linings or in regional lymph nodes and is “processed” by these cells. Either the processed antigen itself or a message from macrophages stimulates B-Lymphocytes produce antigen-specific IgE. The amount of IgE produced depends on the antigen dose, the route of antigen exposure, the number of allergenic sites on the antigenic proteins, and the genetic makeup of the host. In several experimental situations where suppressor T-Cell activity is suppressed, produced increased IgE. Several cell types have surface IgE receptors including basophils, macrophages, mast cells, eosinophils, platelets and lymphocytes. The IgE antibody molecules attached to the cell surface initiate an IgE mediated reaction.

The antigen – antibody reaction on the cell surface elicits intracellular events. In general, the outcome of these intracellular calcium and adenosine

triphosphate dependent events release of various mediators. The classical mediator released by allergic reactions is histamine, which directly causes bronchial smooth muscle contraction and stimulates reflex bronchospasm.

Eosinophilic chemotactic factor of anaphylaxis is another preformed mediator, and metabolites such as prostaglandins, thromboxanes, Leukotriene, platelet activating factor (PAF) likely to play important role in asthma, especially in chronic asthma and late-phase inflammatory reactions. In addition to their immediate effect on smooth muscle, these potent mediators initiate chemotaxis and increased vascular permeability.

Late-Phase Allergic Reaction

This allergic response is characterized by inflammation, edema, bronchoconstriction, and occasional symptoms of fever and malaise. It follows the early response by 4 to 8 hours, without the early response the later one does not occur. PAF, often released from eosinophils has potent inflammatory activity and has been associated with the production of airway hyper reactivity by producing vascular permeability and edema.

DIAGNOSIS OF ASTHMA[2,3,30]

- Asthma is under diagnosed throughout the world.
- Asthma can often be diagnosed on the basis of symptoms such as episodic breathlessness, wheezing and chest tightness. Seasonal variability of symptoms and a positive family history of asthma and atopic disease also helps as diagnostic guides.
- However, measurements of lung function, and particularly the reversibility of lung function abnormalities greatly enhance diagnostic confidence.
- Lung function measurements that are most helpful for the diagnosis of asthma (in patients over 5 years of age) include forced expiratory volume in 1 second (FEV_1) forced vital capacity (FVC), peak expiratory flow (PEF), and airway hyper responsiveness. Among them Peak expiratory flow meter (PEFM) is commonly used in most of the places.

- Measurement of symptoms and lung function are important parameters for assessing the characteristic of the patient's asthma.

Symptoms that are useful when considering a diagnosis of asthma

- attack or recurrent attacks of wheezing
- troublesome cough at night
- Wheeze or cough, chest tightness after exposure to airborne allergens or pollutants
- Colds "go to the chest" or take more than 10 days to clear up
- Symptoms improvement after antiasthma treatment

International Union Against Tuberculosis and Lung disease (IUATLD) Asthma Questionnaire[2,31]

- ❖ Have you had Wheezing or Whistling in your chest at any time?
- ❖ Have you had an attack of shortness of breath that came on following strenuous activity at any time?
- ❖ Have you woken up with an attack of wheezing at any time?
- ❖ Have you woken up with an attack of coughing at any time?

- ❖ Have you had an attack of shortness of breath that came on during the day when you were at rest at any time?

All these things were considered during the selection of cases for the study.

Physical Examination [21,22]

Because asthma symptoms are variable, the physical examination of the respiratory system may be normal. The most usual abnormal physical finding is wheezing on auscultation. However, some people with asthma have normal auscultation but significant airflow limitation when measured objectively.

Clinical signs such as dyspnoea, airflow limitation (wheeze) and hyperinflation are more likely to be present if patients are examined during symptomatic periods. The combination of hyperinflation and advanced airflow limitation in an asthma exacerbation also markedly increases the work of breathing. Although wheezing is the most typical physical finding in asthma, the sign may be absent in severe asthma exacerbations. However, patients in this state usually have other physical signs reflecting severity, such

as cyanosis, drowsiness, difficulty in speaking, tachycardia, hyper inflated chest, use of accessory muscles, and intercostals recession.[32] The classification of severity of asthma exacerbations is provided in table 2.

TABLE 2: CLASSIFICATION OF SEVERITY OF ASTHMA EXACERBATIONS *

	Mild	**Moderate**	**Severe**	**Impending Respiratory Failure**
Symptoms				
Breathlessness	With activity	With talking	At rest	At rest
Speech	Sentences	Phrases	Words	Mute
Signs				
Body position	Able to recline	Prefers sitting	Unable to recline	Unable to recline
Respiratory rate	Increased	Increased	Often > 30/min	> 30 /min
Use of accessory respiratory muscles	Usually not	Commonly	Usually	Paradoxical thoracoabdominal movement
Breath sounds	Moderate wheezing At mid-to-end-expiration	Loud wheezes throughout expiration	Loud inspiratory and expiratory wheezes	Little air movement without wheezes
Heart rate (beats/min)	<100	100 – 120	>120	Relative bradycardia
Pulsus paradoxus (mm Hg)	<10	10-25	Often > 25	Often absent
Mental status	May be agitated	Usually agitated	Usually agitated	Confused or drowsy

Functional assessment				
PEF(% predicted or personal best)	>80	50-80	<50 or response to therapy lasts <2 hours	<50
$Sa0_2$(%, room air)	>95	91-95	<91	<91
$Pa0_2$(mm Hg, room air)	Normal	>60	<60	<60
$PaC0_2$(mm Hg)	<42	<42	≥42	≥42

* Adapted from National Asthma Education and Prevention Program. Expert Panel Report 2: Guidelines for the Diagnosis and Management of Asthma. National Institutes of Health Pub. No. 97-4051, Bethesda, MD, 1997

Measurement of lung function [33,34,35]

Measurement of lung function, particularly the reversibility of lung function abnormalities provide a direct assessment of airflow limitation. Measuring the variability in lung function provides an indirect assessment of airway hyperresponsiveness.

There are wide range of different methods to assess the level of airflow limitation exists, but two methods have found widespread acceptance for use in patients over 5 years of age, are the measurement of forced expiratory volume in 1 second (FEV_1) and its accompanying forced vital capacity (FVC), and the measurement of Peak Expiratory Flow (PEF). Both of these

measurements depend on the concept of airflow limitation relating directly to the luminal size of the airways (airway caliber) and the elastic properties of the surrounding lung tissue (alveoli).

Treatment aspects of Bronchial asthma [36]

The Expert panel of the NAEPP (National Asthma Education and Prevention Program) of the National Heart, Lung and Blood institute has developed asthma classification schemes which are useful in directing asthma therapy and identifying patients at high risk of developing life-threatening asthma attacks.

Approach of Long-term Treatment [37]

Current approaches are based on both the severity of the patient's base line asthma and the severity of asthma exacerbation. NAEPP recommends a stepwise approach to therapy provided below in Table 3.

TABLE 3: STEPWISE APPROACH FOR MANAGING ASTHMA*

	Long-Term Control	**Quick Relief**	**Education**
Step 1: Mild Intermittent	No daily medication needed.	**Short-acting bronchodilator; inhaled β_2 agonists as needed for symptoms.** Intensity of treatment will depend on severity of exacerbation. Use of short-acting **inhaled β_2 agonists > 2** times a week may indicate the need for long-term control therapy.	Teach basic facts about asthma. Teach inhaler/inhalation chamber technique. Discuss roles of medications. Develop self-management & action plans. Discuss appropriate environmental control measures.

* Modified from National Asthma Education and Prevention Program. Expert Panel Report 2: Guidelines for the Diagnosis and Management of Asthma. National Institutes of Health Pub. No. 97-4051, Bethesda, MD, 1997

However, the inhaled forms not available for the study we are taking tablet form of short-acting bronchodilator. The present study was proposed to conduct in mild cases.

Pharmacological Agents for asthma [38,39]

Asthma medications can be divided into long-term and quick-relief medications. Long-term control medications (controller, maintenance or preventive medications) are taken daily to achieve and maintain control of persistent asthma by action primarily to attenuate inflammation.

Quick relief medications are taken to promote prompt reversal of acute airflow obstruction and relief of accompanying symptoms by direct relaxation of bronchial smooth muscles.

A. Long – Term control Medications

In this group the agents mainly used are

1. **Anti inflammatory agent**

   Corticosteroids - Inhaled corticosteroids,
   Systemic corticosteroids

2. **Long – acting bronchodilators**

   a. Mediator inhibitors – cromolyn sodium and nedocromil.

   b. Beta-adrenergic agents – long acting β_2 agonist provide bronchodilation for up to 12 hours after a single dose.

      Salmeterol and formoterol are the two agents commonly used to control nocturanal and exercise induced asthma.

   c. Phosphodiestrase inhibitors [40]

      Theophylline – It provides mild bronchodilatation in asthmatics and may also have antiinflammatory properties, enhance mucociliary clearance, and strengthen diaphragmatic contractility. Theophylline serum

concentrations need to be monitored closely owing to the drug's narrow toxic therapeutic range.

3. Leukotriene modifiers [41]

This is the newest class of medications for long-term control of asthma. Leukotrienes are potent biochemical mediators that contribute to airway obstruction and asthma symptoms. Zileuton is a 5-lipoxygenase inhibitor that decreases leukotriene production. Montelukast are cysteinyl leuktotinase receptor antagonists.

These agents product modest improvements in lung function and reductions in asthma symptoms and lessen the need for beta-agonist rescue therapy. These agents may be considered as alternatives to low dose inhaled corticosteroids in patients with mild persistent asthma.

4. Desensitization

Immunotherapy for specific allergens may be considered in selected asthma patients who have exacerbations of asthma symptoms when exposed to allergens to which they are sensitive and who do not respond to environmental control measures or other forms of conventional therapy.

5. Miscellaneous agents

Oral sustained – release β_2 agonists are reserved for patients with both some nocturnal asthma symptoms or moderate to severe persistent asthma who do not respond to other therapies.

Corticosteroid – sparing antiinflammatory agents such as methotrexate, cyclosporine, intravenous immuno globulin and gold should be used only in selected severe asthmatics.

B. Quick- relief Medications [42]

Short acting bronchodilators and systemic corticosteroids comprise the important medications in this group of agents.

1. Beta – adrenagic agents [43]

Short acting inhaled beta adrenergic agonists are clearly the **most effective** bronchodilators during exacerbations. Beta – adrenergic agonists should be used in all patients to treat acute symptoms. These agents relax airway smooth muscle and cause a prompt increase in airflow and reduction of symptoms. There is no convincing evidence to support the use of one agent over another. However, **β2-selective agents** produce less cardiac stimulation than those with mixed β1 and β2 activities. Currently available short acting β2-selective adrenergic agonists

include Salbutamol (albuterol), bitolterol, pirbuterol and terbutaline. Inhaled beta-adrenergic agonist therapy is as effective as oral or parenteral therapy in releaxing airway smooth muscle and improving acute asthma and offers the advantage of rapid onset of action (<5 minutes) with fever systemic side effects. Intravenous and subcutaneous routes of administration should be reserved for patients who because of age or mechanical factors are unable to inhale medications.

2. Anticholinergics [44]

Anticholinergic agents reverse vaguly mediated bronchospasm but not allergen or exercise - induced bronchospasm . They may decrease mucous gland hypersecretion seen in asthma.

Ipratropium bromide, a quaternary derivative of atropine free from atropine side effects, is the only available agent. This drug reverses acute bronchospasm and is the inhaled alternative for patients with intolerance to β2 agonists. It is the drug of choice for bronchospasm due to beta – blocker medications.

3. Glucocorticoids [45]

Systemic Corticosteroids are effective primary treatment for patients with moderate to severe exacerbations (or) for patients who fail to respond promptly and completely to inhaled β2

agonist therapy. They are one of the main stays of the treatment of patients with severe asthma. These medications speed the resolution of air flow obstruction and reduce the rate of relapse.

4. Antimicrobials [22,23]

Antibiotics have no role in routine asthma exacerbations. They may be useful if bacterial respiratory tract infections are thought to contribute. Thus, patients with fever and purulent sputum and evidence of pneumonia or bacterial sinusitis are reasonable candidates.

COMPLICATIONS [41]

The Complication of asthma include

- Exhaustion
- Dehydration
- Airway infection
- Cor pulmonale
- Tussive and
- Syncope
- Pneumothroax – but is rare
- Acute hypercapnic and hypoxic respiratory failure in severe disease

COMPLEMENTARY ALTERNATIVE MEDICINES [46]

For the purpose of Review the complementary alternative medicine used for the treatment of asthma is provided below.

Home remedies - Natural treatment for asthma

a. Honey (Shahad)

b. Garlic (Lahsoon)

c. Turmeric (Haldi)

d. Bitter guard (Karela) root

e. Figs (Anjeer) dry

f. Indian gooseberry (Amla)

g. Linseed (Alsi)

h. Mustard (Rye) oil

i. Dietary considerations

j. Other measure

    1. Take enema to clear colon to prevent autotoxication.
    2. Application of mud-pack to the abdomen.
    3. Wet chest packs and steam bath.
    4. Breathing exercises, dry climate
    5. Mild physical exercises and correct posture

k. Management of Bronchial asthma with Herbomineral, Ayurvedic Drugs.

l. Salt therapy for Asthma [47]

It is not a new concept – inhaling the salt air steam from heating salt solution was recommended treatment from the days of Hippocrates.

m. Spleotherapy[48] or Underground climatotherapy is an alternative treatment for asthma used mostly in Eastern Europe.

PREVENTIVE ASPECT [23,38]

Patient Education

Patient education is a necessary component to successful management of both acute and chronic asthma. It

- need to realize the repetitive and progressive nature of their asthma and
- educate them to live safely and as symptom – free as possible and
- Motivated to learn the pathophysiology of asthma, factors triggers (e.g) Avoid contact with allergens, Avoid aspirin NSAID agents when possible.
- Oriented towards Medication actions and side effects.
- Motivated to monitor there airway function objectively by expiratory peak flow measurements

- thoroughly familiarized themselves with the proper use of inhaled bronchodilators and spaces.
- Patients and their physicians need to recognize, and allow them to the emotional impact of asthma on their lives and families.

  Only through open, unrushed and empathic communication can the physician open the door to this important interaction.

Vaccination

Patients with persistent asthma should receive the Pneumococal vaccine (Pneumovax) and annual influenza vaccinations.

Dietary considerations as followed in complementary alternative medicines

In dietary considerations the patients should avoid the common dietic errors. Ideally, diet should contain limited acid forming foods like carbohydrates, fats and proteins and a liberal quantity of fresh fruits, green vegetables and germinated gram. Foods tend to produce phlegm such as rice, sugar, lentils and curds as well as fried and other difficult to digest foods should be avoided. Asthmatics should always eat less than their capacity.

Do's and Don't in Bronchial asthma in Ayurveda [16]

* Do not have chilled cold drinks, ice creams etc.,

* Do not have fish / fish products

* Do not have excessive oily and spicy pungent food

* Do not sleep at very Late night

* Do not have tension or stress

* Do not have any self medicine

* Take medications regularly without any gap

Research area in bronchial asthma [4,6]

A few reports document the usefulness of these medications. The research areas are:

1. Effect of erythromycin as a mucolytic agent
2. Effect of furosemide by altering the sodiumchloride membrane transport system
3. Atrial natriuretic factor
4. Glucagon effects under trial
5 . Omalizumab –first biological drug approved for bronchial asthma a recombinant human monoclonal antibody targetting IgE antibodies

MATERIALS AND METHODS

SETTING

The present study was carried out in the outpatient department of thoracic medicine, Government Rajaji Hospital, Madurai.

COLLABORATING DEPARTMENTS

This study was carried out in collaboration with

- Institute of Pharmacology,
- Department of Thoracic Medicine, and
- Department of Biochemistry

DESIGN OF STUDY

It was a open label, single centre, randomized comparative trial.

STUDY DURATION [August 2004 – March 2006]

1. Literature collection – 3 months
2. Designing the study – 1 month
3. Case selection and drug administration – 12 months
4. Analysis and follow up – 2 months

5. Interpretation – 1 month
6. Discussion – 2 months

SAMPLE SIZE

Total sample was 50 (25+25) cases, those who satisfied a rigid inclusion and exclusion criteria.

ETHICAL APPROVAL

Institutional ethical clearance was obtained from the ethical committee, Government Rajaji Hospital, Madurai [Annexure I]. Letter No: 1419/E4/3/04/ O/o. Dean, GRH, Madurai dated 27-01-2005

INFORMED CONSENT

Informed consent was obtained from all the patients. They were personally explained, dated and signed in duplicate by both patient and the investigator [Annexure II].

SELECTION OF STUDY SUBJECTS (i.e. cases)

Patients of both sexes suffering from mild asthma [as per GINA table-2) attending thoracic medicine outpatient department selected by the professor

Department of Thoracic Medicine, Government Rajaji Hospital, Madurai. By using peak expiratory flow meter (PFM), the PEFR was recorded. They were started on salbutamol inhaler (100mg/puff) 2 puffs at 10 minutes interval and the difference in the improvement before and after inhalation was recorded by using PFM. Those who showed improvement in PEFR more than 15% or >200ml were selected for study.

INCLUSION CRITERIA FOR THE PRESENT STUDY ARE:

*** subjects with asthma (GINA-mild)**

Patients who were grouped / classified under mild asthma as per GINA were considered for the study because of the following reasons.

1. They can be managed with single molecule.
2. Easy to convince for the study.
3. Unlikely to develop disease related complications, emergencies.

*** Age group (25-40 years)**

Patients within 25-40 yrs of age group were selected because

- They can be made to understand easily
- They will cooperate better for follow up

- Of economical independence.

*** Subjects with PEFR - performance**

Only those patients who showed an improvement of 15% after inhalational bronchodilator therapy were included.

*** Subjects willing for the study**

Subjects were explained about the proposed study, the need for follow up and the necessity to follow a healthy life style. Only those subjects who accepted to adhere to this guideline were considered for the study.

*** BMI ranges from 19-23**

Those patient's whose BMI was within 19 to 23 were considered so as to have homogeneity as well as to have uniform pharmacokinetic parameter, and they are unlikely to have abnormal lung function.

*** Literacy state**

At least patients with ability to read and write Tamil were included in order to follow home care instructions carefully.

EXCLUSION CRITERIA

The patient who had any one of the following (or) a combination of them was excluded.

*** Age 25 - 40**

Subjects of less than 25 yrs may be less cooperative and those above 40 yrs might be suffering from the disease for longer duration (or) may be hailing disease related complications, co-morbid conditions.

*** Unwilling / non-compliance**

Those not willing to participate (or) who did not have the intention the consent for compliance were excluded.

Personal habits

*** Tobacco users – smoking, alcohol, drug addiction**

Smokers both active and passive, Alcohol consumers and drug addicts (e.g. Cannabis indica) were excluded.

*** Those practicing yoga, pranyama (or) breathing exercise**

As their yogic exercise will influence the air flow, those practicing such were excluded.

*** Physiological status**

Special restrictions for female patients

The hemodynamic changes and hormonal variations during the physiological status – pregnancy, women in periods & nursing female patients were excluded.

*** Hematological aspects**

As Anemia (or) other hematological disorder contribute to breathlessness, those cases were excluded.

*** Respiratory system**

Severe bronchial asthma, COPD, respiratory infection, eosinophilia pulmonary tuberculosis (old & active) pulmonary hypertension, thoracic abnormalities, and patients undergone previous lung volume reduction surgery were excluded.

*** Cardiovascular system**

Those with hypertension, cardiac disease or pericardial disease were excluded.

*** Endocrine and metabolic system**

Those with diabetes mellitus, hypothyroidism, obesity were excluded.

*** GIT**

Gastroesophageal reflux disorder (GERD), ascitis, liver disease, because GERD can induce asthma by triggering airway narrowing in susceptible persons.

*** Renal system**

Those with acute (or) chronic renal problems were excluded.

*** Immune system**

Those on steroids, HIV/AIDS, renal transplantation.

***Central nervous system**

Those with neuro-psychiatric illness, unconscious, and nonambulant were excluded.

*** Connective tissue disorders**

Collagen disease and Autoimmune disease were excluded.

*** Concomitant medication**

Those patients consuming complementary and alternative medicines internally or consuming analgesic agents were excluded.

*** Previous participation**

Those who participated in similar drug trial elsewhere were excluded.

*** Others**

Patient subjected to thorough systemic examination were excluded if any one of the systemic abnormalities were identified.

*** DISCONTINUATION CRITERIA**

Patients were permitted to discontinue from the study, once they were decided to do so. Patient when found to develop other illness (or) worsening of the existing illness (or) requiring additional drugs, they were withdrawn from the study.

CASE SELECTION

Thus, 50 cases were selected over a period of 6 months. Counselling was given to them on the proposed study for this purpose. Patients were informed verbally and in writing by the investigator about the nature,

significance, implications and risks of the study prior to enrollment. All items were explained by the investigator in a language and in terms that were easy to understand by the patient. Informed consent was obtained for all patients personally dated and signed by both the patient and investigator. The details of the investigator (name, phone number, and contact address) were given to each and every patient, to enable them to contact for any ailments at anytime during the study period.

CONDUCT OF THE STUDY

Visit 0 (V_0)

Patient information sheet and informed consent procedure as well as inclusion and exclusion criteria were considered

Data collection

Following data were collected.

Socio-demographic data

In this, name, age, sex, address, education qualification, occupation, living environment, working place environment, travelling time to reach hospital were collected.

Medical History

- H/o present illness
- H/o previous drug intake
- H/o associated allergic disorder
- Allergic rhinitis
- Eczema
- Atopy
- H/o occupational exposure to
    - Smoke
    - Chemical
- Family History
- H/o similar illness in their family
- Personal history
- Smoking
- Veg / Non-veg

*** Physical examination**

Height / Weight / BMI

*** Laboratory Investigation**

Blood samples were collected from each patient for determination of the following parameters.

- ❖ Complete blood count
- ❖ Biochemical investigation
- ❖ Haemoglobin
- ❖ Blood sugar, urea
- ❖ Serum creatinine
- ❖ Serum potassium
- ❖ Renal function test
- ❖ Urine analysis

*** Micro biological investigation**

Sputum examination for gram stain and AFB stain were done.

*** Image science**

1. X-ray chest PA view after deep inspiration – to rule out any other lung abnormalities
2. ECG was taken to assess cardiac status .

TABLE 4: STUDY MEDICATION, DOSAGE AND STORAGE

Details of the drugs	**Racemic salbutamol**	**Levosalbutamol**
Brand Name Batch no.	Asthalin (Cipla) 4mg M.LDD/L/235 B.No. DJ 5118	Levolin (cipla) 2mg M.L.616 B.No. X40160
Manufacturing date & . Expiry date	4mg – mfd – May 04 Exp Apr - 08	Oct – 2004 } Sep – 2006 } for 2mg
Drug formulation & Strength & package	Tablet 4mg/ blister pack	Tablet 2mg / blister pack
Route of administration	Oral	Oral
Dosage Regimen and intake	3 times a day after food	2 times a day after food
Cost	4mg/Rs.5.14 per 10 tablets	2mg/Rs.8 per 10 tablets

Labelling of study medication

The stripes of tablets were cut into single units and the required number of tablets for 15 days were placed in a cover were given to the patient on visit 0 and they were asked to bring empty blister packs for pill counting. They did not have any concomitant chest diseases. They were assuring not to take any supportive or concomitant medication. While they were on these drugs, they were advised not to take any other medications without the knowledge of investigator.

Start of Treatment and Instruction of Patients

Treatment started on the day of visit 0. The date of first administration of the study medication was documented in the corresponding schedule of visists. Instructions were given to the patient to adhere to those instructions Each patient was advised to return the used blister packs at visit 1 in order to maintain accountability of study medication.

Adverse effects:

Patient were given a card carrying details of adverse effects in Vernacular language as shown below and motivated them to mark the side effects / experienced during drug therapy on a meticulous manner. These cards were analysed during review visit of the patient.

∗ Overdose

Clinical sign of intoxications were explained instructions were given to avoid overdose.

∗ Patient Assessment

With reference to the aim the patients were assessed for pulmonary function by simple instrument peak flow meter before and after drug administration at weekly intervals, the details were recorded.

*** Pulmonary function assessment**

- Instrument used – peak flow meter
- Frequency – before and after drug at weekly intervals

*** Clinical Assessment**

Pulse rate, respiratory rate, blood pressure and side effects were evaluated.

*** Biochemical assessment**

- Blood collection for serum potassium level before and after drug administration was done following standard precautions.

Financial Support

The funds required for the purchase of drugs were made available by the funds contributed by the Department of thoracic medicine and

pharmacology. Patients follow up and incentives provided by the above funds.

Study monitoring, auditing and inspections

In order to ensure adherence to the guidelines, audit and inspections were done by thoracic department and pharmacology department.

Outcome of the study

Outcome of the study was assessed by clinical improvement, symptom assessment, bio chemical investigations and pulmonary function tests.

Statistical Analysis

The effect of drug therapy is analysed by paired ‘t’ test. Patients age, gender, pulmonary function and adverse effects were subjected to statistical analysis.

RESULTS

In this study there were 11 males and 14 females in racemic salbutamol group, and 10 males and 15 females in levosalbutamol group. The age ranged from 25 to 40 in racemic salbutamol group, and 23 to 39 years in levosalbutamol group. The BMI of both groups varied from 19 to 23 and the mean was 21. Economicial status in both the category ranged from 600 to 900 rupees/month. The clinical data, ECG, X-ray chest and Haematology were nil contributory. However, they had episodes of wheezing over a period of 5 years. The details are provided in table 5.

TABLE 5: CHARACTERISTICS OF STUDY POPULATION

Basic Characteristics	Racemic Salbutamol	Levosalbutamol
Gender		
Male	**11**	**10**
Female	**14**	**15**
Age in years		
Range	**25-40**	**23-39**
Median	**31**	**30**
±SD	**4.69**	**4.31**

BMI	**19 – 23**	**19-23**
Mean	**21**	**21**
Economical status		
Range in Rupees.	**600 – 900**	**600 – 900**
Clinical data		
ECG	**Nil Contributory**	**Nil Contributory**
X-ray Chest	**Nil Contributory**	**Nil Contributory**
Hematology	**Nil Contributory**	**Nil Contributory**

Distribution of cases in relation to age and gender are shown in Table 6 for racemic salbutamol and levosalbutamol given below

TABLE 6: DISTRIBUTION OF CASES IN RELATION TO AGE AND GENDER

Age in years	Levosalbutamol			Racemic Salbutamol		
	Male	Female	Total	Male	Female	Total
25-39	3	6	9	3	5	8
30-34	4	5	9	5	5	10
35-40	4	4	7	3	4	7
Mean	32.59	32.23	32.32	32.5	32.41	32.4
SD	0.79	0.86	1.19	0.74	0.89	1.16
Median	28.12	26.0	29.5	27.5	27.0	27.25

Not significant in relation to age between these groups

The past history of allergic disorder [35] in the form of nasal stuffiness, sneezing, itching over the skin, utricarial rashes were noticed in 3 among 25 in racemicsalbutamol group and 5 among levosalbutamol group. Family history of similar allergic illness was found in 2 and 1 among racemic salbutamol and levosalbutamol groups respectively. Renal function test and liver function test did not reveal any abnormalities.

TABLE 7: DISTRIBUTION OF CASES IN RELATION TO ALLERGIC DISORDER AND FAMILY HISTORY

Sl.No.	Clinical / Lab	Racemic Salbutamol (n=25)	%	Levo Salbutamol (n=25)	%
1	H/o. patients associated with allergic disorders	3	12	5	20
2	Family H/o. similar illness	2	8	1	4
3	Renal function test*	Within normal limits		Within normal limits	
4	Liver function test **	Within normal limits		Within normal limits	

* serum creatinine ** serum enzymes bilirubin, albumin, globulin

Pulmonary function with PEFR before and after oral administration of Racemic Salutamol and levo salbutamol are provided in Table 8.

TABLE 8: PEAK EXPIRATORY FLOW RATE COMPARISON AMONG TWO MOLECULES OF SALBUTAMOL

PEFR	Racemic Salbutamol		Levo Salbutamol	
	Mean ± SD	Median	Mean ± SD	Median
Before	249.6 / 66.36	220.0	254.8 / 50.59	175.29
After	265.2 / 64.10*	250.0	309.6 / 55.94**	202.94

*Significant P = 0.0047 **p = 0.0000175

The patients were grouped into those receiving racemic salbutamol as group I and those receiving Levosalbutamol as group II. The mean PEFR before and after therapy in group I was 249.6 and 265.2 respectively and the mean in group II was 254.8 and 309.6 respectively. The pulmonary function improved significantly (table 8) after oral exposure to salbutamol irrespective of the type. However the improvement was very high in the levosalbutamol group (p=0.0000175) thus indicating the levosalbutamol has better effect as bronchodilator. Of the biochemical test, serum potassium level among the study groups both before and after revealed some changes. The serum potassium level among these cases before and after salbutamol was provided in table 9. In both the categories potassium level at the end of 2 weeks was slightly more than what it was in the beginning. The details are provided in table 9.

TABLE 9: SERUM POTASSIUM LEVEL BETWEEN THE STUDY GROUPS

Sl. No.	Groups	Potassium Level	Before	After	Significance
1	Racemic Salbutamol	Mean ± SD Median Mode	4.1 ± 0.4397 4 4	4.204 ± 0.6024 4 4	Not significant
2	Levo Salbutamol	Mean ± SD Median Mode	4.208 ± 0.4349 4.2 4	4.28 ± 0.5156 4.24 4	Not significant

The nature of side effects observed in both the groups were provided in table 10. Tachycardia, tremor and muscle cramps were significantly low in levosabutamol group.

TABLE 10: NATURE OF SIDE EFFECTS

Sl. No	Side Effects	Racemic Salbutamol (n=25)	%	Levo Salbutamol (n=25)	%	Significance
1	Palpitation	10	40	2	8	0.0063
2	Muscle Cramps	10	40	3	12	0.0213
3	Tremor	17	68	3	12	0.00001
4	GERD	3	12	0	0	-
5	Polyurea	2	8	0	0	-

Side effects Significantly less with levo salbutamol

DISCUSSION

Bronchial asthma is a disease known for centuries and description is made in different systems of Medicine. Despite enormous advances in the management of asthma, till we do not have any definitive drugs. However, salbutamol is one of the commonly used bronchodilator in day to day practice.

Systematic name of Salbutamol is (±) alpha 1-[(tert-butylamino)methyl]-4-hydroxy-m-xylene-alpha, alpha'-diol. The generic class of the drug is beta2-adrenergic bronchodialator. It is included under FDA drug as Antiasthmatics / Bronchodilators. The molecular formula of Salbutamol is $C_{13}H_{21}NO_3$ and the molecular weight is 239.31g/mol. The melting point is 157-158^{0}C (with decomposition). Salbutamol is a white or almost white, crystalline powder when dissolved in methanol the solution is clear and very pale yellow in colour. Solubility of Salbutamol is sparingly soluble in water; but soluble in ethanol (96%); and slightly soluble in ether also. [49]

It has C, H, N & O molecules and the percentage of the same was 65.25%,8.84%,5.85%, 20.06% respectively and it is marketed in almost all countries under different brand names. It is available as single molecule or in combination. In India Salbutamol marked as either in single molecule or in

combinations with various drugs like Corticosteroids in various drug formulations. Some of them were mentioned below:

Salbutamol available in India in various drug formulations and marketed by different companies in simple or as sustained release or controlled release form etc.,

Tablet form: E.g., Asthalin, Salbetol, Salmaplon, Bronkotab.

Syrup form: E.g., Salbu, Asthalin, Ventrolin

Capsule: E.g., Salbair Trans-Cap

Rotacap: E.g., Asthalin

AC-Inhaler/MDI: E.g., Asthalin

Combination Formulations:

Rotocap/MDI : E.g., Aerocart (Salbutamol 200mcg+ Beclomethasone dipropioate 100mcg)

HFA Inhaler: E.g., Asthalin

Duolin Inhaler/MDI: E.g., Ipratropium Bromide 20mcg, Salbutamol 100mcg

Bronchilet: E.g., Salbutamol, Hydroxy ethyl Theophylline 124mg

The market price of salbutamol as a lone molecule vary from 10 paise to 35 paise for a strength of 2mg, 16 paise to 52 paise for 4mg tablet and for 90 paise to Rs.1.25 paise for 8mg.

Salbutamol was developed from the modification of Norepinephrine, a natural neurotransmitter. Norepinephrine stimulates α and β adrenoceptors in the body, a more specific drug was need that targetted only the β adrenoceptors. It was found that the replacement of one hydrogens on the amine with a isopropyl group produced isoproterenol (isoprenaline) which has increased stimulation of β adrenoceptors whilst a reduce stimulation of α adrenoceptors. However Isoproterenol was not metabolically stable and was inactivated by the enzyme catechol O-methyltransferase too quickly to be usefully used in the treatment of asthma. Another disadvantage was the there are two types of β adrenoceptors, β_1 and β_2, isoproterenol activated both receptors The activation of β_1 adrenoceptros in the cardiovascular system gave rise to side effects such as palpitations and cardiac arrhythmia. [50,51]

This widespread, regular use of beta$_2$ agonist drugs as a class, particularly in the absence of inhaled corticosteroids, could potentially lead to worsening asthma control. This may be due to rebound airway hyperresponsiveness; as a result the patient might require higher doses, resulting in incidence of beta-mediated side-effects like tachycardia, tremors, hypokalaemia etc.,[52] All this has led to relook at the available beta$_2$-agonists to develop more safer and therapeutically active agents. Synthetic β_2-agonist bronchodilators are developed based upon the structure of epinephrine and are

thus supposed to mimic the bronchodilating action of epinephrine. However, endogenous epinephrine is a pure single isomer (R) – epinephrine, whereas most of the β_2 – agonists including salbutamol are racemates. Salbutamol is racemic compound composed of a 50:50 mixture of two non superimposable mirror image isomers.

Although Salbutamol was first synthesized in 1969 there is still much research into better, quicker and more efficient syntheses of R-Salbutamol. There is currently only one major synthesis of R-Salbutamol although there are many possible ways of producing pure samples of R-Salbutamol via distereomeric resolution.

In the present study the clinical improvement in the form of improved PEFR was noticed after exposure to oral levosalbutamol which was highly significant (P=0.0000175) in contrast to racemic salbutamol. Since inhaled form of levosalbutamol was used in many studies in different countries, it was taken into consideration for comparative analysis with present work. In the present study the variability in serum potassium level was noticed after administration of drug by different authors and the comparative analysis is shown in the table 11 below.

TABLE 11. COMPARATIVE ANALYSIS WITH REFERENCE TO PULMONARY FUNCTION

Sl. No.	Author, Year, Country, Number of cases, Study type	Outcomes	Key results	Study weaknesses
1	Lipworth Bjet al, 1997, **UK** **n=12** **PCRT**	Tremor, plasma potassium, heart rates were measured	Potassium values (p values not provided)	Small sample size.
2	Gumbhir Shah K et al, 1999, **USA** **n=13** **RCT**	FEV_1 plasma, potassium, heart rate	No change in plasma potassium levels	Small sample size
3	Lotvall J etal, 2001, **Sweden** **n=20** **PCRT**	FEV_1 heart rate and plasma potassium levels. Side effects	Rapid increase in plasma potassium level No serious adverse events	Small sample size.
4	Pancu D et al, 2003, **USA** **n=27** **RDBPCT**	Serum potassium values at baseline Side effects	No difference between any group. No side effects. Levosalbutamol caused fewer side effects	Potassium is uncertain and these changes may not be applicable.
5	Present Study 2004, **Madurai** **n=25** **RSBCT**	PEFR, serum potassium values, heart rate Side effects: muscle cramps, palpitation, tremor, GERD, poly urea	Significant improvement in Levo salbutamol group.	Side effects less in levosalbutamol.

PCRT - Placebo control randamised trial
RDBPCT - Randamised double blind placebo control trial
RSBCT - Randamised single blind control trial

The reasons for variable levels in serum potassium among different population could be due to dietary variation, renal clearance of potassium and pharmaco kinetics of levosalbutamol as well as genetic contribution for potassium level in the body. In addition initial serum potassium level might have also contributed. Moreover, the serum potassium level was carried out at two different occasions and this might also have contributed. [53,54]

Several studies have suggested an association between Beta agonist use and an increased risk of death from asthma. Proposed mechanisms include increased bronchial hyperresponsiveness, drug tolerance or an underlying increased severity of disease. Such analyses support the continued use of salbutamol as a first line therapy for the treatment of asthma.

This apparent controversy appears to be due to the two different isomers have opposing effects. R-Salbutamol causes smooth muscle to relax whereas S-salbutamol causes smooth muscle to contract. The two isomers act on different receptors and thus on different pathways resulting in the opposing effects.

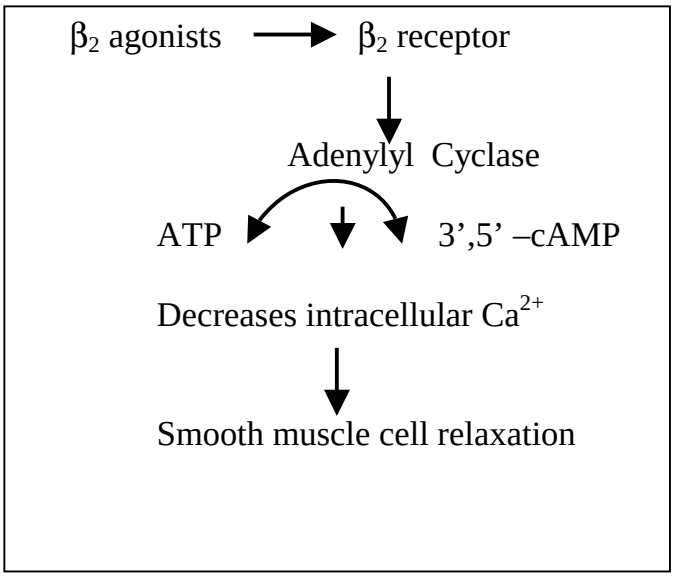
S-salbutamol is now thought to be the main cause of bronchial hyper responsiveness in the treatment of asthma with salbutamol. S-salbutamol acts on muscarinic receptors. There are also G linked proteins and also have seven trans membrane domains. Being a G linked protein the conformational changes and the dissociation of the alpha sub unit is identical to that of the beta two receptor. However the alpha sub unit activates a different enzyme in this pathway. In this pathway the alpha sub unit activates phospholipase C. This enzyme catalyses the phosphorylation of Phosphatidylinositol 4,5-bisphosphate (PIP_2) to inositol 1,4,5-triphosphate (IP_3) on the inside of the membrane. This small molecule (IP_3) is no longer bound to the membrane and leaves the plasma membrane and diffuses through the cytosol. In the cytosol it releases Ca^{2+} from the endoplasmic reticulum (ER) by binding to IP_3 gated Ca^{2+} release channels in the ER membrane or ryanodine receptors in the sarcoplasmic reticulum of muscle cells. This initiates a positive feedback system as the Ca^{2+} released can bind back to the channels releasing more Ca^{2+}. Thus S-salbutamol initiates a sudden increase of Ca^{2+} ions which initiates

muscle contraction, which contributed to more side effects / adverse reactions.[55]

In view of the opposing effect, research were made to isolate R-Salbutamol from the racemic mixture. The mechanism of muscle relaxation due to R-Salbutamol furnished below. R-Salbutamol acts on Beta 2 Adrenergic Receptors. These receptors are found on the smooth muscle lining airways of the lungs. The binding of R-salbutamol to this receptor causes a conformational change in the protein. β2 adrenergic receptors are an example of a G linked protein, the receptor has seven trans membrane domains and is associated in the membrane with a G protein. The G protein has three sub units (an alpha sub unit tightly associated beta and gamma sub units). The conformational change in the β2 receptor causes in the G protein. A guanosine 5'-diphosphate (GDP) group associated with the G protein becomes dissociated and is then replaced with guanosine 5'-triphosphate(GTP) group. This is turn causes the alpha sub unit to dissociate from the G complex. The dissociated alpha sub unit is then free to move in the membrane and has a binding site for the enzyme adenylyl cyclase. It binds to an adenylyl cyclase

and activates it. This enzyme catalyses the conversion of ATP to cAMP (adenosine5;-triphospahte to adenosine 3',5'-monophosphate). cAMP levels in the cell therefore increase due to the additional adenylyl cyclase produced by the binding of R-salbutamol. cAMP activates protein kinase A (a cyclic AMP dependent protein kinase). Protein kinase A transfers the terminal phosphate group of an ATP to several target proteins within the cell which leads to muscle relaxation. [49]

Mechanism of Action of β_2 agonists is described in pictorial manner below



The phosphorylation process leads to muscle relaxation by several processes including active removal of Ca^{2+} ions from the cell and into intracellular stores, thus lowering intracellular Ca^{2+} ion concentration. Ca^{2+} led to inhibition of Phosphoinositid hydrolysis which inturn led to direct inhibition of myosin light chain kinase activity, thus opening of calcium activated potassium channels that repolarises smooth muscle cells. Muscle concentration is initiated by a sudden rise in cytosolic Ca^{2+} ions concentration and reduced cytosolic Ca^{2+} concentration will cause muscle relaxation. [56]

Thus R-salbutamol can cause muscle relaxation irrespective of the method of initiation of the muscle contraction (the contractile agent, be it neural or mediated). As asthma is caused by many different contributions leading to muscle contraction and makes salbutamol a suitable drug for its treatment.

R salbutamol also has several other beneficial effects on the lungs (other than smooth muscle relaxation) and they are

a. Inhibition of mast cell mediator release

b. Increases mucous secretion and

c. Increased clearing of the mucus by the action of cilia.

However R-salbutamol has no effect on chronic inflammation. Through the inhibition of mast cell mediator release, which is anti-inflammatory, R-salbutamol can to an extent also modify acute inflammation an another

symptom of asthma. In the present study the PEFR improved remarkably as observed by other authors. This salbutamol contributes to relaxation of smooth muscle of bronchi and thereby improves the pulmonary function. In general the component of S-Salbutamol in racemic form causes smooth muscle to contract. Interestingly two isomers that is R-Salbutamol, S – Salbutamol act on different receptors in different pathways resulting in opposing effects. The mechanism of opposing effects is in contradiction to expectation is furnished below.

In the present study side effects such as muscle cramps, palpitation, tremor, GERD and Polyurea were more among racemic than levo salbutamol group. Studies have found peak plasma concentrations occur approximately 2 to 5 minutes after inhalation and 2 to 2.5 hours after ingestion. Salbutamol is metabolized in the liver, mainly by conjugation to the inactive salbutamol-4'-0-sulphate. Salbutamol's plasma half life is reportedly 2.7 to 5 hours after oral administration. The half life has been indirectly estimated through urine excretion studies to be 3.8 hours after inhalation. Unchanged drug and metabolite are 72% excreted in the urine within the first 24 hours. R-Salbutamol being an analog of human (R) – epinephrine is a more natural substrate for the sulfotransferase enzymes and therefore is more rapidly sulphated and eliminated than (S) – Salbutamol. Accordingly markedly elevated plasma levels of (S) – Salbutamol are seen after dosing with racemic

salbutamol. This is a major concern when repeated dose of racemic salbutamol are administered, which might lead to accumulation of (S) – Salbutamol and which might be responsible for worsening of the disease, considering the detrimental effects that have been reported with (S)-Salbutamol. Levosalbutamol appears to be stereochemically stable in vivo and does not appear to interconvert metabolically to (S) – salbutamol. [57, 58]

The difference between the action of leveosalbutamol versus racemic salbutamol in relation to cellular, experimental and clinical properties are provided in table 12 given below:

TABLE 12: CELLULAR, EXPERIMENTAL AND CLINICAL PROPERTIES OF (S) AND (R) SALBUTAMOL *

Properties	(S) Salbutamol	(R) – Salbutamol
Receptor Binding	Does not bind to β_2 receptors	Specifically binds to β_2 receptors
Calcium concentration	↑Intracellular calcium concentration	↓Intracelluar calcium concentration
Eosinophil	↑Eosinophil activation	↓Eosinophil activation
Histamine	↑Histamine-induced epithelial permeability ↑Always protein, neutrophils, and IL8	↓Histamine-induced epithelial permeability ↓Always protein, neutrophils, and IL8
Airway response	↑Airway tissue response to spasmogens	↓Airway tissue response to spasmogens

Tissue response	Difficult to metabolize; unnatural molecule.	Easy to metabolize; natural analog
Accumulation	Accumulates with regular dosing	Shows no evidence of accumulation
Therapeutic effect	Demonstrates no bronchodilatory effect	Achieves all therapeutic bronchodilatory effect
Pulmonary function test	Not inert: may be clinically detrimental	Does not diminish lung function with chronic use
Bronchodilatory potency	↓Overall racemic bronchodilator potency	↑Overall bronchodilatory potency

↑ increases or enhances ↓ reduces or inhibits
* Source: FDA Medical Reviewer, 1999

(S) salbutamol not only fails to relax airway smooth muscles but under certain circumstances may augment bronchoconstriction; Increased intracellular calcium in airway smooth muscle and bronchial hyper responsiveness; activates phospholipase C and induces calcium influx into airway smooth muscle, changes that could lead to bronchial hyperresponsiveness.

From the present study it is clear that oral form of levosalbutamol has distinct advantage for those patients suffering from bronchial asthma. The observations were supported with available literature since the cellular, experimental and clinical properties of R – Salbutamol are superior to S-Salbutamol, a component of racemic salbutamol. Hence, it is suggested that

levosalbutamol (R-Salbutamol) may be used in day to day clinical practice for the patients who are in need of the same.

The **strength of the study** was, a rigid inclusion criteria, close monitoring and supervision by specialists, and regular follow up with subjective and objective means.

However, there were **limitations** as in any study and they were

a. Post study follow up not done,
b. Observer bias single blind
c. Arterial blood gas analysis not done and spirometry not used due to technical constrains.
d. Pharmacokinetic studies not done
e. No cross over study done and
f. Nebulised form not used

CONCLUSION

The following conclusions were arrived,

a. The efficacy and tolerability of Levosalbutamol was better than Racemic salbutamol.

b. Side effects were less in the Levosalbutamol group.

c. Highly significant improvement in PEFR was noticed in those used Levosalbutamol.

d. In view of the clinical and therapeutic advantage observed among the patients with mild bronchial asthma, oral form of Levosalbutamol is recommended for such cases.

SUMMARY

Bronchial Asthma is known for time immemorial. Variety of therapeutic agents though available in different systems of medicine, modern scientific medicine try to act at the cellular level to some extent with constraints.

Among the modern pharmacological agents use for bronchial asthma, salbutamol is included in the WHO's essential drug list. However, the available form is in racemic form with inherent side effects. A newly available oral form such as levosalbutamol (R-salbutamol) is shown to have better than conventional one. Hence, the present study was undertaken

1. To compare the efficacy and tolerability of Racemic salbutamol and Levosalbutamol.
2. To identify the side effects of each, and to recommend the appropriate one

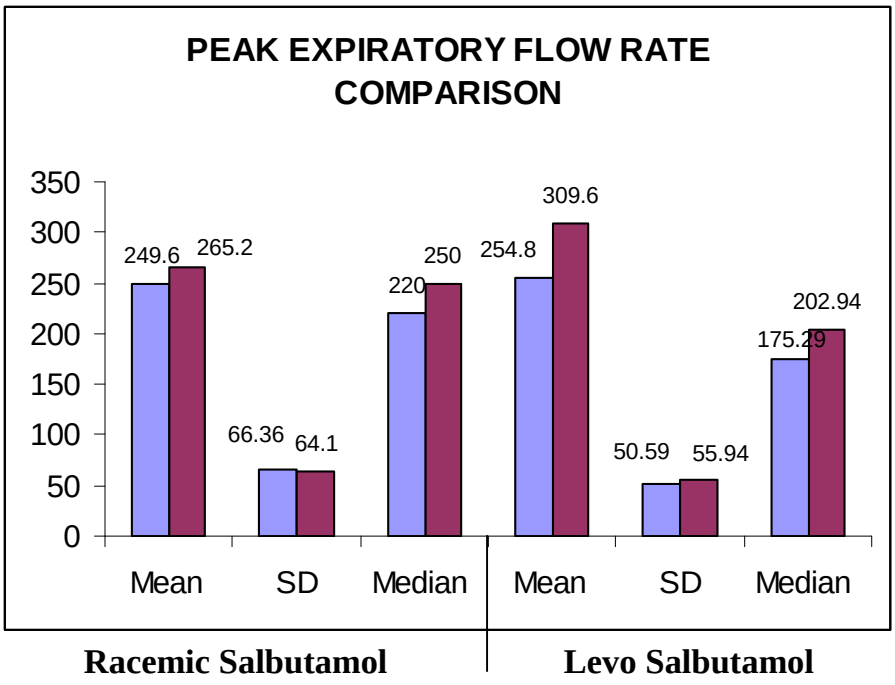
After the institutional ethical clearance and informed consent, a single blind open label randomized comparative trial was attempted among 50 (25 in

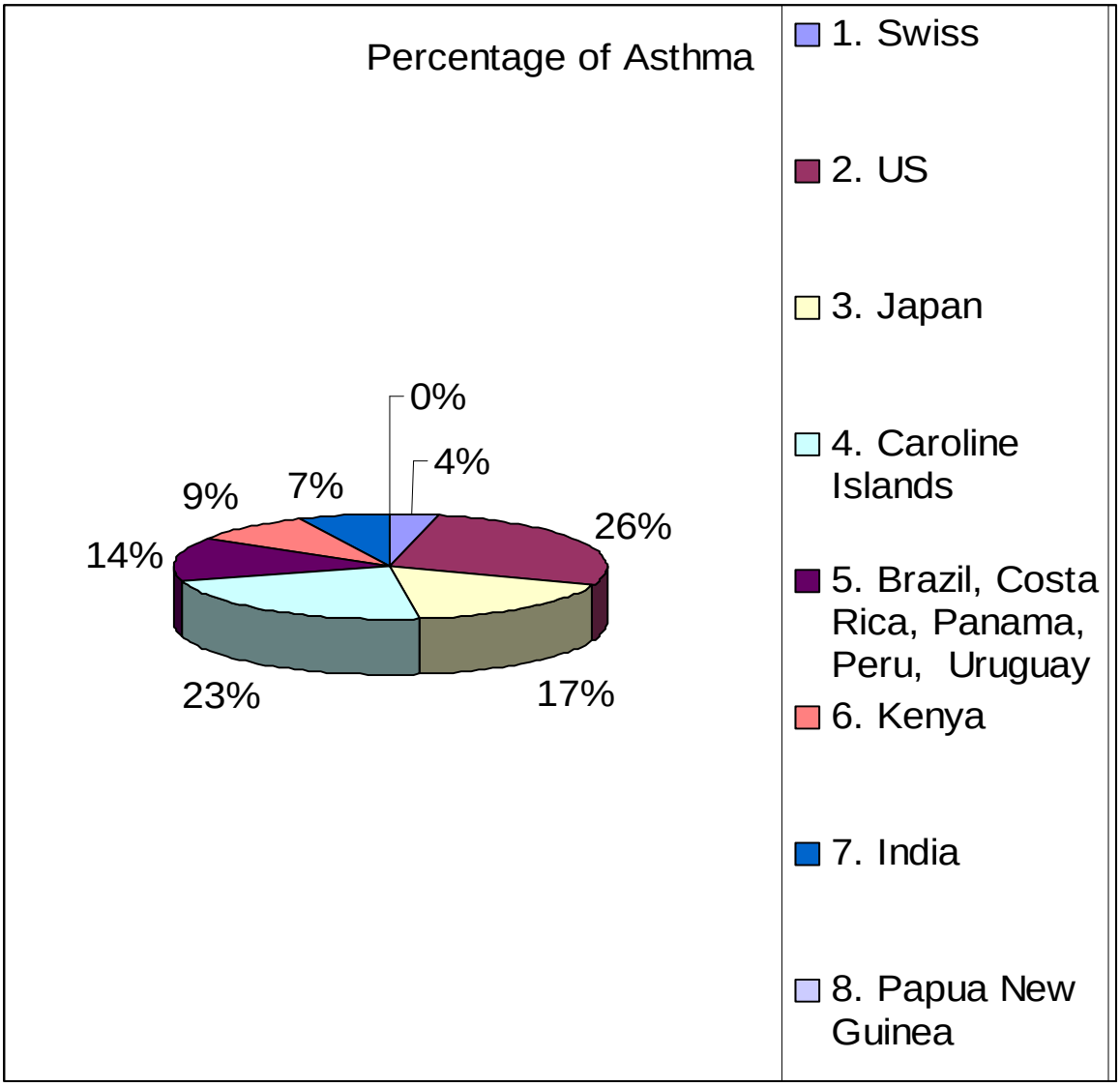
each group), mild bronchial asthma patients who satisfied a rigid inclusion and exclusion criteria. Their socio demographic, clinical, and laboratory data were collected. They were trained, counselled and explained about the study and were given respective salbutamol orally after food. Subjective and Objective assessment (using PEFR) were made along with side effects. The data were analysed statistically.

There were 11 males and 14 females in racemic salbutamol group, and 10 males and 15 females in levosalbutamol group. The age ranged from 25 to 40 in racemic salbutamol group, and 23 to 39 years in levosalbutamol group. The BMI of both groups varied from 19 to 23 and the mean was 21. They had episodes of wheezing over a period of 5 years, there hematology, bio chemical tests, liver function test, renal function test, X-ray, ECG were nil contributory. The patients were grouped into those receiving racemic salbutamol as group I and those receiving levosalbutamol as group II. The mean PEFR before and after therapy in group I was 249.6 and 265.2 respectively, and the mean in group II was 254.8 and 309.6 respectively. The pulmonary function improved significantly (Table 8) after oral exposure to salbutamol irrespective of the

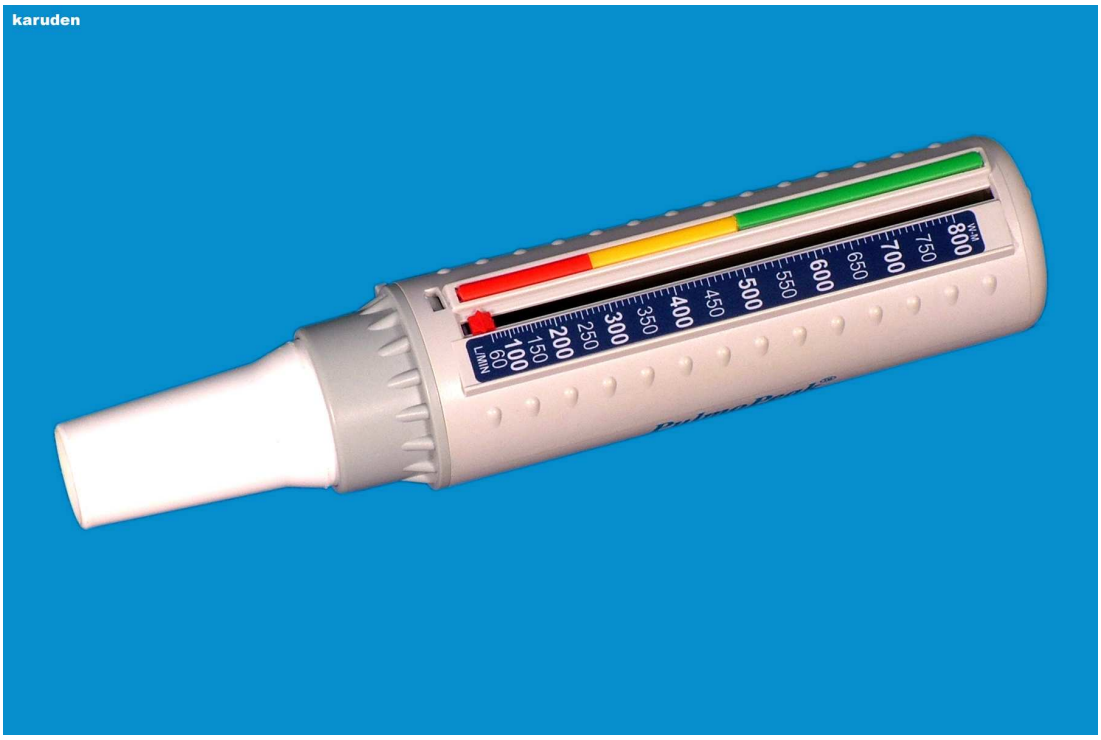
type. However the improvement was very high in the levosalbutamol group (p=0.0000175), thus indicating the levosalbutamol has better effect as bronchodilator. Side effects were negligible in levosalbutamol group. There was no gross alteration in serum potassium level after therapy.

In view of the efficacy, tolerability and significant improvement in PEFR with negligible side effects observed among levosalbutamol group, it is recommended that oral levosalbutamol can be used for those with mild bronchial asthma.


PEAK EXPIRATORY FLOW RATE COMPARISON
350
300
250
200
150
100
50
0
249.6
265.2
66.36
64.1
220
250
254.8
309.6
50.59
55.94
175.29
202.94
Mean
SD
Median
Mean
SD
Median
Racemic Salbutamol
Levo Salbutamol

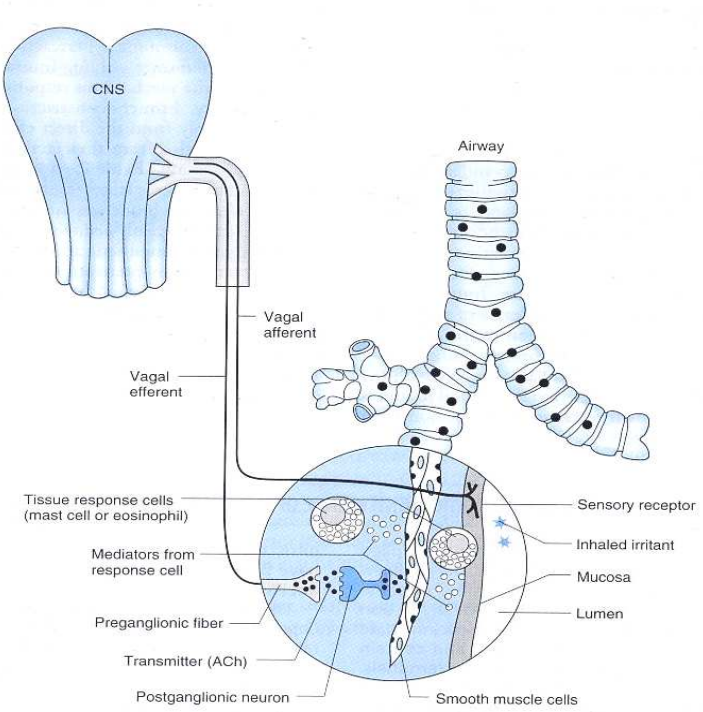

Percentage of Asthma
0%
4%
7%
9%
14%
26%
23%
17%
1. Swiss
2. US
3. Japan
4. Caroline Islands
5. Brazil, Costa Rica, Panama, Peru, Uruguay
6. Kenya
7. India
8. Papua New Guinea

PEAK FLOW METER

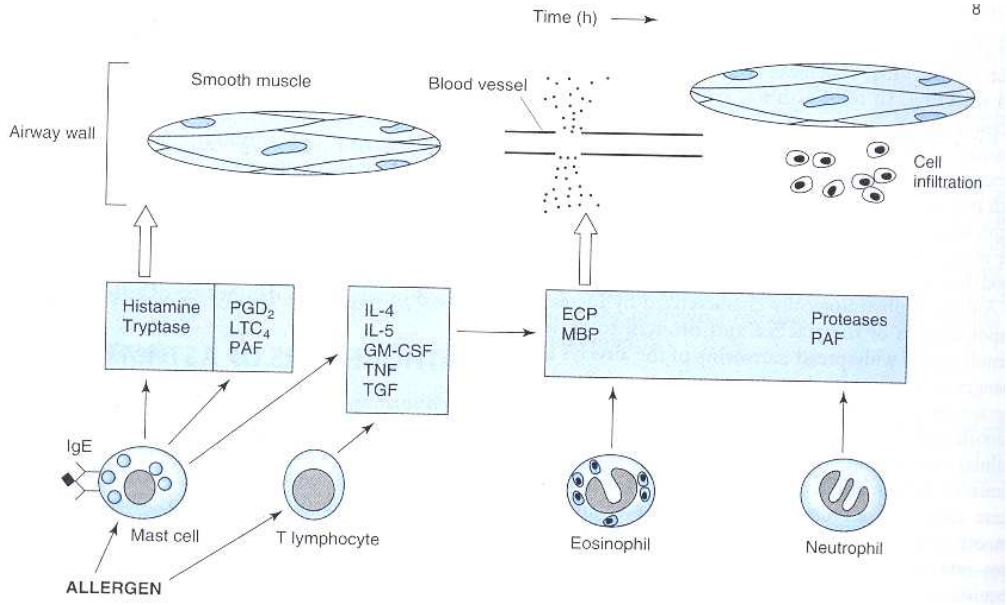


PEAK FLOW METER
PERFORMANCE

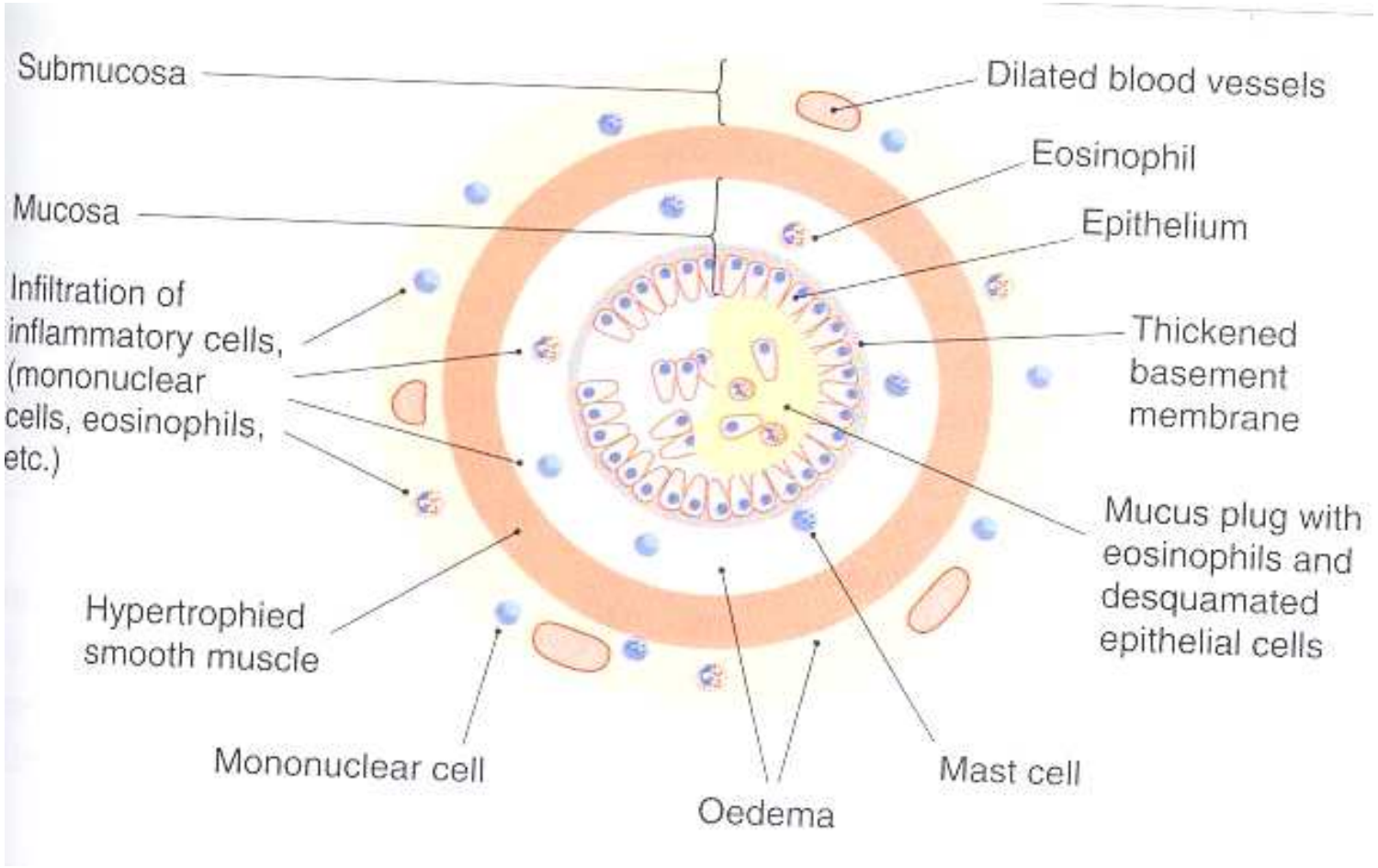
MECHANISMS OF RESPONSE TO INHALED IRRITANTS



CONCEPTUAL MODEL FOR THE IMMUNOPATHOGENSIS OF ASTHMA



SCHEMATIC DIAGRAM OF A CROSS-SECTION OF A BRONCHIOLE SHOWING CHANGES OCCUR WITH ASTHMA

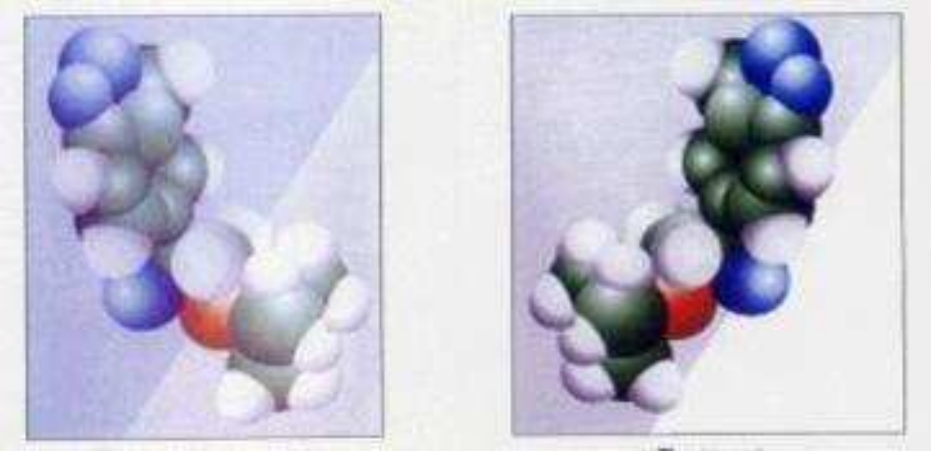


RACEMIC SALBUTAMOL

50:50 Mixture of Mirror – image isomer

(S) – isomer
(Dextrosalbutamol)

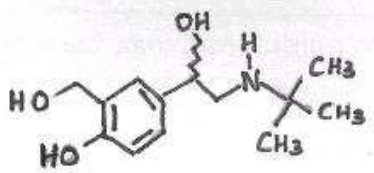
(R) – isomer
(Levosalbutamol)



Little or no adrenoreceptor activity

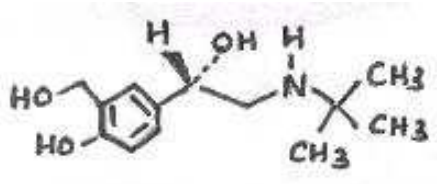
Potent β_2 adrenoreceptor stimulant

MOLECULAR STRUCTURE OF SALBUTAMOL

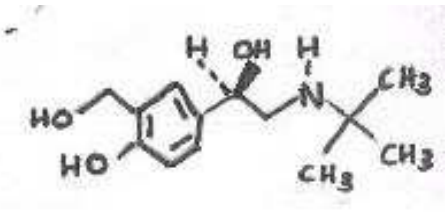


ISOMERS

R-SALBUTAMOL



S-SALBUTAMOL



ANNEXURE I

346/pharmacology
16/2/05

Ref.No. 1419/E4/3/04 Dated: 27.1.05 of the
Dean, Govt. Rajaji Hospital, Madurai.

Minutes of the First Ethical Committee Meeting for the year 2005 held at 12.30 P.M. on 2.2.05 at the Deans Chamber, Govt. Rajaji Hospital, Madurai.

The following members of the Committee were attended the meeting.

1) Dean incharge/Chairman of Ethical Committee
2) Prof. of Medical Oncology
3) Prof. of Surgical Oncology
4) Prof. of Obst. & Gynaecology
5) Director, Institute of Pharmacology
6) Prof. of Opthalmology
7) Prof. of Medicine.

The member of the Ethical Committee approves the following projects.

Name	Project	Remarks
1. Prof. and H.O.D. Dept. of Medicine Govt. Rajaji Hospital	Histopathologic studies of nature valves from autopsy samples	Approved/Permitted
2. Prof .and H.O.D. Dept. of Medicine Govt. Rajaji Hospital, Madurai.	Bullying among Medical students	Not permitted
3. Prof. and H.O.D. Dept. of Obst. & Gynaec. Madurai Medical College, Madurai.	ICMR Study on Randomised Controlled Clinical Trial with Praneem Polyherbal Tablet and Standard treatment for abnormal Vaginal discharge.	Approved/Permitted
4. Prof. and H.O.D. Dept. of Medicine Madurai Medical College, Madurai	Dietary and anthro pomatic aspects among patients with coronary heart diseases	Approved/Permitted
5. Dr.C.Ravindranath Asst. Prof. of Psychiatry. Govt. Rajaji Hospital, Madurai.	Psychiatry Morbidity in l Medica Oncology	Approved/permitted
6. Dr.S.Kanatha Pandian Reader and Head of Bio Tech. Alagappa University. Karaikkudi	To obtain bacterial and fungalsamples from Opthalmology department,. GRH., Madurai	Approved/permitted

02265

7. Dr.K.Raadhika P.G.Student, Pharmacology, Madurai Medical College, Madurai.	Bronchodilators in bronchial Asthma.	Approved/permitted
8.Dr.V.Theivanai. P.G.Student, Pharmacology Madurai Medical College, Madurai	Pharmacological challenges in Anti-Retro viral Therapy	Approved/permitted
9. Dr. V.Anand. P.G.Student in M.D) (General Madurai Medical College, Madurai.	Serum Calcium level in newly diagnosed Hypertension	Approved/permitted
10. Prof. and H.O.D. of Medicine, GRH, Madurai.	Identification of slow and rapid acetylators among T.B. population	Approved/permitted
11. Mr. Minashi Kumar Mr.Girhani Lal Dayal III MBBS., MMC, Madurai	Congenital Heart diseases in ICMR & RC,GRH, Madurai.	Approved/permitted
12. Prof and H.O.D. of Medicine, Govt. Rajaji Hospital, Maduai.	Mortality study in Primary Hyperoxaluria	Approved/permitted

Endt.No:2265 /E1/4/05 Dt. 15-02-2005

Note:

1) All those are doing project or research work are instructed to submit a detailed summary of their work to the ethical committee on completion of the work.
2) All those who are involved in their work should duly acknowledge the ethical approval in their work.
3) The project or research work should be limited for which the ethical committee has given approval.
4) They should not violate ethical approval and limits/regulations.
5) If any modification is not approved, requires a fresh application.

Forwarded

ADMINISTRATIVE OFFICER
For Dean
Madurai Medical College
Madurai - 625 020.

DEAN/CHAIRMAN
Ethical Committee
Govt. Rajaji Hospital,
Madurai.

To
Dr. K. Raadhika
P. G. Student
Pharmacology
Madurai medical college - Thro. Proper channel.

ANNEXURE II

Informed Consent Form in English

Full name of the patient (in capital letters): _____

Address: _____

Date of birth: _____ Patient Number: _____ Sex: _____

I freely agree to participate in the above-mentioned clinical study.

My doctor _____ informed me in a personal counseling interview about the study drug, possible side effects and risks, the nature, objective and significance of this clinical study, and my responsibilities resulting thereof, In addition, I read and understood the contents of the Patient Information Sheet and the Informed Consent Form. The doctor answered all questions in an adequate and comprehensible manner.

I had sufficient time to decide on my participation in this clinical study.

I will follow the instructions of my doctor, which are essential for the performance of this clinical study. I have the right to withdraw from the study at any time without giving any reason and without any disadvantage for me.

I confirm that I have not participated in this study and I have not taken part in another study within the last 30 days prior to the start of the study.

I received one original of the Patient Information Sheet together with the signed Information Consent Form.

_____

(Place, date and Signature of the patient)

_____

(Place, date and Signature of the doctor)

ANNEXURE III

PATIENT INFORMATION SHEET

Who can be contacted for further questions?

For further questions regarding this clinical study or your rights as patient and participant in the study, please contact your doctor, who will always be ready to provide you the necessary information.

If you have experienced any health-related problem as well as in case of hospitalization please contact your doctor.

Name and address of Contact Person: _____

_____

Phone Number: _____

Please take a copy of this information sheet home with you.

ANNEXURE IV

INFORMED CONSENT FORM IN TAMIL

நோயாளியின் பெயர்:_____ வயது:_____ இனம்: _____
விலாசம்: _____

தகவல் அளிக்கப்பட்ட ஒப்புதல் படிவம்

மேற்குறிப்பிட்ட மருத்துவ ஆய்வில் ஓர் பங்கேற்பாளராக சேர்க்கப்பட இதன் மூலம் நான் சுதந்திரமாக என் ஒப்புதலை அளிக்கிறேன்.

ஆய்வு மருந்து பற்றி ஒரு தனிப்பட்ட ஆலோசனை நேர்முக விளக்கத்தில் என் ஆய்வு மருத்துவர் ஆய்வு மருந்து, சாத்தியமாகும் விளைவுகள் மற்றும் அபாயங்கள், இயல்பு, இந்த மருத்துவ ஆய்வின் நோக்கம் மற்றும் முக்கியத்துவம் பற்றி மற்றும் அதனால் ஏற்படும் எனது பொறுப்புகள் பற்றி எனக்கு தகவல் தெரிவிக்கின்றார். இதோடு கூடுதலாக, நான் ..... தேதியிட்ட எனக்கு அளிக்கப்பட்ட நோயாளிக்கான தகவல் தாள் மற்றும் தகவல் அளிக்கப்பட்ட ஒப்புதல் படிவத்தில் அடங்கிய விபரங்கள் பற்றி படித்து புரிந்து கொண்டுள்ளேன். மருத்துவர் போதிய மற்றும் விரிவான விதத்தில் என் அனைத்துக் கேள்விகளுக்கும் பதில்கள் அளித்துள்ளார். இந்த மருத்துவ ஆய்வில் என் பங்கேற்பு பற்றித் தீர்மானிக்க எனக்குப் போதிய நேரம் இருந்தது.

இந்த மருத்துவ ஆய்வு நடத்தப்பட மிக முக்கியமானதாக என் மருத்துவரின் குறிப்புகளை நான் பின்பற்றுவேன். எந்த காரணமும் அளிக்காமல் , எனக்கு எந்த நஷ்டமும் ஏற்படாமல் எந்த நேரத்திலும் ஆய்வை விட்டு விலக எனக்கு உரிமை உண்டு.

இந்த மருத்துவ ஆய்வில் சேகரிக்கப்படும் எனது சொந்த தகவல் , குறிப்பாக எனது மருத்துவ ரெகார்டுகளில் எனது பெயர் மற்றும் பாலினம் மற்றும் இனம் குறிக்கப்படும் என்பதற்கு நான் சம்மதிக்கிறேன் இந்த தகவல் ஆனது

* எலக்ட்ரானிகல் முறையில் அல்லது ஒரு பகுதி காகித வடிவில் பதிவு செய்யப்படும் பத்திரமாக வைக்கப்படும் மற்றும் மதிப்பீடு செய்யப்படும்

* விஞ்ஞான மதிப்பீடு மற்றும் கூடுதல் விஞ்ஞான உபயோகத்துக்காக மற்றும் அளிக்கப்படும்.

* உகந்த தேசிய மற்றும் சர்வதேச ரெகுலேட்டரி அதாரிட்டிகளுக்கு அனுப்பப்படும்.

.இதோடு மட்டுமின்றி அங்கீகரிகப்பட்ட பிரதிநிதிகள் எனது சொந்த விபரங்கள் உடனான மருத்துவ ரெகார்டுகளை பரிசோதிக்கலாம். விஞ்ஞான மதிப்பீடு

மற்றும் மருத்துவ ஆய்வின் செயல் திறனுக்காக தகவலை முழுமையாக சரியாகப் பரிமாற்றம் செய்ய இது உதவுகிறது.

நான் இந்த ஆய்வில் இதுவரை பங்கேற்று இருக்கவில்லை மற்றும் இந்த ஆய்வு ஆரம்பிக்கும் முன்பு 30 நாட்களில் நான் மற்றொரு ஆய்வில் பங்கேற்றிருக்கவில்லை என்பதை உறுதி செய்கிறேன்.

நோயாளிக்கான தகவல் தாளின் ஒரு அசல் உடன் கையெழுத்திடப்பட்ட தகவல் அளிக்கப்பட்ட ஒப்புதல் படிவத்தை நான் பெற்றுள்ளேன்.

நோயாளி:

_____ _____ _____

பெயர் பெரிய எழுத்துக்களில் கையெழுத்து தேதி

சாட்சி:

_____ _____ _____

பெயர் பெரிய எழுத்துக்களில் கையெழுத்து தேதி

நோயாளிக்கு உறவு முறை: _____

நான் டாக்டர் ..... மேற்கண்ட பெயருடைய நோயாளிக்கு ஆய்வின் நோக்கம் மற்றும் தன்மை பற்றி விளக்கியுள்ளேன் என்பதை உறுதி செய்கிறேன். மேலும் நான் அனைத்து ஆய்வு சம்பந்தப்பட்ட கேள்விகளுக்கும் பதில்கள் அளித்துள்ளேன். மற்றும் ஆய்வின் நிபந்தனைகளை (மற்றும் ஏற்படலாம் எனும் விளைவுகள்) அவர்களுக்கு விளக்கியுள்ளேன் என்பதை உறுதி செய்கிறேன்.

மருத்துவர் டாக்டர்:

_____ _____ _____

பெயர் பெரிய எழுத்துக்களில் கையெழுத்து தேதி

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ADVERSE EFFECTS CARD

Starting Date	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
1. MUSCLE CRAMPS (கால் சதை பற்றி இழுத்தல்)							
2. TREMOR (கை நடுக்கம்)							
3. H/o. Palpitation (படபடப்பு)							
4. GERD (நெஞ்செரிச்சல்)							
5. POLY UREA (அடிக்கடி சிறுநீர் கழித்தல்)							
6. Insomnia, Restlessness (தூக்கமின்மை)							
7. Any Other (வேறு ஏதேனும் உடல் உபாதை புதிதாக தோன்றினால் எழுதவும்)							

Checked by the Investigator **Signature**

Date