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COMPARATIVE STUDY OF TERBUTALINE AND SALMETEROL DRUGS IN TREATMENT OF ASTHMA

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ABSTRACT

Asthma is a common condition due to chronic inflammation of the lower respiratory tract. Asthma is a condition in which your airways narrow and swell and produce extra mucus. This can make difficult to breathing. In some cases, it may lead to a life- threatening attack. it may cause chest pain, breathlessness, chest tightness, shortness to breath and cough particularly produced at night or early in morning "Asthma is a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role: in particular, mast cells, eosinophils, T lymphocytes, macrophages, neutrophils, and epithelial cells. In this review we have studied about the asthma, its symptoms, causes and drugs used in the treatment of asthma. There are different drugs which are used in the treatment of asthma but in this article, we have explained some of the drugs and these drugs are: Aminophylline, Montelukast, Zafirlukast, Hydrocortisone, prednisolone, Terbutaline and salmeterol. Ipratropium bromide, Tiotropium bromide, Theophylline

KEYWORDS: Asthma, inflammation, airway, Receptor, bronchodilators.

INTRODUCTION

Asthma management might mean different things to different people. The patient experiences shortness of breath, coughing, and/or wheezing on an intermittent basis.[1] For the parent, the appearance of symptoms in their child could entail missed workdays or restless nights. In the eyes of the doctor, asthma is a complicated illness that manifests in a variety of phenotypes that might differ according to age, gender.[2] Asthma "attacks" can also vary in frequency and intensity between and among patients. They can be brought on by a variety of factors, such as

exposure to aeroallergens, viral infections, exercise, irritants, certain drugs (like aspirin), and gastroesophageal reflux. According to the pathologist, mucus hypersecretion and airway inflammation are the hallmarks of asthma.[3]

To aid in clinical care and research, educational institutions have attempted to define "severe asthma."Given the difficulty in diagnosing asthma and the paucity of evidence supporting a cl ear severe asthma phenotype, this is a difficult task.[4]

In this study, we go over the need for a definition of severe asthma as well as the relative adv antages of the various attempts that have been made in the past to come up with one.

The inability to distinguish between severity and control, the variability of phenotype in sever e asthma, and the possibility of misclassification are all emphasized.[5]

We come to the conclusion that, while likely to persist, the quest for a single definition of sev ere asthma is problematic.

We recommend the substitute. Asthma genetics is a new and complex subject and is assumed to be caused by a combination of genes, and our present understanding of the genetic risk factors for asthma development is being expanded by quickly evolving technologies.

We will just give a basic overview of this complicated subject here.

Our knowledge of the genes that predispose people to asthma has significantly increased than ks to genome-wide association studies (GWAS).[6]

Etiological agents of asthma

Low-molecular-weight (LMW) substances and high-molecular-weight (HMW) (glyco)proteins derived from plants and animals are examples of workplace agents that are known to induce allergic OA.[7] The known IgE-mediated process is how HMW proteins and a few LMW substances (such as reactive dyes, platinum salts, acid anhydrides, sulfonechloramide, and certain wood species). The majority of LMW agents, such as isocyanates, persulphate salts, aldehydes, and wood dusts, have effects that are not entirely explained by the immunological pathways.

Types of Asthma

- Allergic asthma
- Non-Allergic asthma
- Exercise-induced asthma
- Nocturnal Asthma
- Cough-Variant Asthma (CVA)
- Severe Asthma

Allergic Asthma

Among asthma phenotypes, allergic asthma is the most prevalent.

It usually is defined by the presence of sensitization to environmental allergens, although a cli nical correlation between exposure and symptoms further supports the diagnosis.

The average age of onset of allergic asthma is younger than that of nonallergic asthma.[8]

Although the spectrum of allergic asthma may vary from mild to severe, studies have reporte d that allergic versus nonallergic asthma is less severe.

There is an increased prevalence of allergic rhinoconjunctivitis and atopic dermatitis in patien ts with allergic asthma.[9]

While there is a significant overlap in levels between the two groups, allergic asthma typically has higher total IgE levels than nonallergic asthma.

Increased Th2 cytokines have been demonstrated in secretions and peripheral blood of patients with allergic asthma.

Non- Allergic Asthma

Those individuals with asthma who do not exhibit allergic sensitization are included in the cat egory of nonallergic asthma.

These people should have negative results from an in vitro specific-IgE test or a skin prick test against a panel of seasonal and perennial allergens. 10% to 33% of people with asthma have nonallergic asthma, which is more common in women and develops later than allergic asthma.[10]

Compared to allergic asthma, nonallergic asthma often seems more severe and may not respond as well to conventional treatment.

While many immunopathologic characteristics of nonallergic asthma are similar to those of allergic asthma, several distinctions have been noted, such as increased GM-CSF and RANTES expression in mucosa and bronchoalveolar lavage fluid.

- **Exercise induced asthma**

After intense activity, the airways temporarily narrow, a condition known as exercise-induced asthma (EIA).

It is believed that the effects of heating and humidifying huge amounts of air during exercise are the mechanism via which EIA takes place.[11]

Although airway cooling was recognized as a significant EIA trigger in 1978, severe EIA alsohappened when hot, dry air was breathed without any aberrant airway cooling.

According to the 1986 thermal hypothesis, the airways narrowed after exercise because cooling had to be followed by a quick rewarming.[12] This caused vasoconstriction, reactive hyperemia of the bronchial microcirculation, and edema of the airway wall.

In people with exerciseinduced asthma, chilly air, low humidity, and hyperventilationwhich isnot always related to exercise—cause an asthma attack.

Increased bronchovascular permeability, bronchial mucosal injury, and increased airway resistance are the results.

The production of mediators such histamine, leukotrienes, nitric oxide, sensory neuropeptides, regulation of neuronal activity, and bronchovascular permeability is the mechanism behind these alterations.

It is uncertain what causes asthma and asthma brought on by activity.

It is most likely a change in local adrenergic function or an anomaly of vascular regulation in the peribronchium.

- **Nocturnal asthma**

An asthma attack that occurs at night is known as nocturnal asthma[13], and it is linked to deteriorating lung function, increased airway reactivity, and an increase in symptoms and treatment requirements.

Since the fifth century A.D., it has been known that most asthmatics experience nighttime ast hma flare-ups, which are thought to be rather common.

Circadian rhythms, which affect inflammatory cells and mediators, hormone levels, and choli nergic tone, are closely linked to the mechanisms of nocturnal asthma.[14]

Individuals who suffer from nocturnal asthma symptoms may have elevated vagal tone, decreased epinephrine, and enhanced activation of inflammatory cells and mediators at night.[15] Furthermore, some patients may be less responsive to treatment due to underlying variations in their b-and glucocorticoid receptors. Sleep is not necessary for nocturnal asthma, but it doe seem to beinvolved in its pathogenesis.[16] Medication can be made more effective and less pois-onous by scheduling it carefully. Leukotriene-modifying drugs, long-acting b-agonists, sustained release theophylline, oral and inhalation corticosteroids, and anticholinergic drugs are among the available treatments.

- **Cough-Variant Asthma (CVA)**

The pathophysiology of cough variant asthma is poorly understood.

In particular, the mechanisms that cause different symptoms in typical asthma (in which whee ze predominates) compared with cough variant asthma (in which cough predominates) have n ot been determined.

Traditional explanations include higher wheezing thresholds, abnormalities in cough sensitivi ty, and/or differences in small airway function.[17]

Recent investigations using high-dose methacholine challenge testing imply that altered small-airway function plays a role. A key pathophysiologic distinction between methacholine- induced cough with normal sensitivity, eosinophilic bronchitis, cough variant asthma, and asthma may be the preservation or loss of the bronchoprotective effect of a deep inspiration.

The most frequent reason why patients seek medical care is a cough, and persistent cough is aparticularly significant clinical issue.

Several nations have released guidelines for the diagnosis and management of cough.

More than 40% of patients in Japan have cough variant asthma, which is one of the most prev alent causes of persistent cough worldwide.

Although it only manifests as coughing, it shares several pathophysiological characteristics w ith classic asthma with wheezing, including atopy, airway hyperresponsiveness, eosinophilic airway inflammation, and different aspects of airway remodeling.

However, without proper treatment, up to 30% to 40% of adult patients may experience whee zing before developing classic asthma.

The ability of coughing to respond to bronchodilators (theophyllines and beta-agonists) is crucial for diagnosing cough variant asthma.[18]

As is known with classic asthma, inhaled corticosteroids are the primary line of treatment if a diagnosis is made.

Recent retrospective studies have demonstrated that this medication relieves cough and may also lower the likelihood of developing classic asthma.

- **Severe Asthma**

Although less than 10% of people with asthma have severe asthma, these individuals bear a d isproportionate amount of the disease's morbidity and medical expenses.[19]

Accurately identifying the patients most at risk for negative outcomes, such as medication side effects, ED visits, hospitalization, near-fatal events, or disability from chronic lung function abnormalities or persistent symptoms, is a major challenge in the diagnosis and treatment of severe asthma.

We need to learn more about the mechanisms underlying severe disease in order to treat these people more effectively.

In order to accomplish this, a uniform definition of severe asthma must be created in order to adequately characterize the condition clinically and to enable comparison of findings from numerous studies.

The age of patients, the age at which the disease first manifested, corticosteroid resistance, persistent airflow obstruction, and biopsy-based evidence of eosinophilic airway inflammation have all been used to characterize a number of severe asthma phenotypes.

Because of these characteristics, there is growing interest in using noninvasive techniques to track airway inflammation in people with severe asthma.

Algorithms for treating severe asthma that are based on indicators of airway inflammation may reduce health care use metrics.[20]

- **Symptoms of Asthma**

- Tobacco smoke
- Dust mist
- Outdoor air pollution
- Pests (e.g, cockroaches, mice)
- Pets
- Mold
- Cleaning and disinfection

- **Triggers of Asthma**

- Animal allergen
- Pollen allergen
- Physical activity
- Air pollution
- Infection

- **Anti-Asthmatic drugs**

Asthma is a chronic inflammatory illness of the airways that is characterized by bronchoconstriction, inflammation, and increased mucus production. Anti-asthmatic therapies are medications used to treat, control, and prevent its symptoms.[21] By focusing on various

facets of the illness, these medications aid in both short-term symptom relief (rescue therapy) and long-term management (preventive therapy).

➢ **Classification of anti-asthmatic drugs**

- **BRONCHODILATORS**

Beta-2 sympathomimetics: Salbutamol, Terbutaline, Bambuterol, Salmeterol.

Methylxanthines: Theophylline, Aminophylline, Choline theophyllinate, Hydroxyethyl theophylline, Doxophylline.

Anticholinergics: Ipratropium bromide, Tiotropium bromide.

- **LEUKOTRIENE ANTAGONIST:** Montelukast, Zafirlukast.

- **MAST CALL STABILIZERS**: Sodium cromoglycate, Ketotifen.

- **CORTICOSTEROIDS**

Systemic: Hydrocortisone, prednisolone and others.

-Inhalational: Beclomethasone dipropionate, Budesonide, Fluticasone propionate, Flunisolide, Ciclesonide.[22]

Bronchodilators

Bronchodilators are a class of drugs that work by relaxing and widening the smooth muscles around the lungs' airways, or bronchial tubes.[23] This relaxation aids in lowering airway resistance, enhancing airflow, and easing symptoms like coughing, wheezing, and shortness of breath. Asthma, chronic obstructive pulmonary disease (COPD), chronic bronchitis, emphysema, and other lung disorders where airway narrowing is a major problem are among the respiratory ailments that are frequently treated and managed with bronchodilators.[24]

These drugs work by interacting with various receptors or pathways to either stop or reverse bronchoconstriction, which is the narrowing of the airways. Bronchodilators are divided into three primary categories based on how they work: Methylxanthines, Beta-2 Adrenergic Agonists, and Anticholinergics (Muscarinic Antagonists)

➢ **Beta-2 Adrenergic Agonists**

These medications relax the muscles and dilate the bronchial tubes by activating beta-2 adrenergic receptors in the smooth muscle of the airways. These are separated into:

- Short-acting beta agonists (SABA)

- Long-acting beta agonists (LABA)

➢ **Short-acting beta agonists (SABA)**

These are also known as Rescue inhalers, offer immediate, temporary relief from severe respiratory problems.

➢ **Long-acting beta agonists (LABA)**

Prolonged bronchodilation is provided with long-acting beta agonists (LABA) as a maintenance treatment.

Terbutaline

Terbutaline is a short-acting β_2-adrenergic receptor agonist (SABA) used as a bronchodilator to relieve and prevent bronchospasms in asthma, chronic bronchitis, and emphysema. It works by stimulating β_2-adrenergic receptors in the airway smooth muscles, leading to bronchodilation, improved airflow, and relief from asthma symptoms like wheezing, coughing, and shortness of breath.

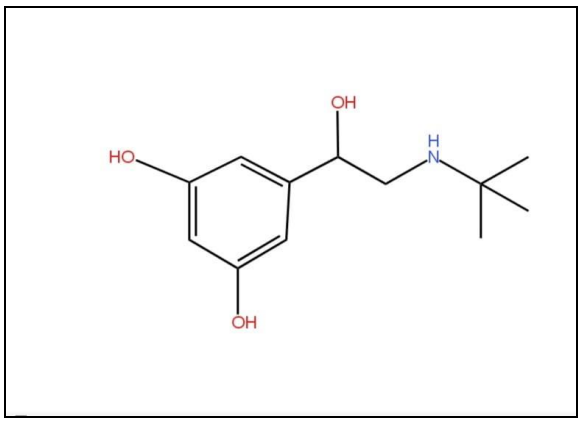

Fig. 1: Represent the structure of Terbutaline.

Mechanism of Action

1. **β_2-Receptor Stimulation:** Terbutaline binds to β_2-adrenergic receptors on bronchial smooth muscles.
2. **Activation of Adenyl Cyclase:** Increases cyclic AMP (cAMP) levels.
3. **Relaxation of Smooth Muscles:** Leads to bronchodilation and improved airflow.
4. **Inhibition of Mediator Release:** Reduces mast cell degranulation, decreasing inflammation and mucus production.

Indications in Asthma

- **Acute Bronchospasm:** Quick relief of asthma attacks.
- **Exercise-Induced Bronchospasm (EIB):** Used as a preventive medication before exercise.
- **Chronic Asthma:** As a part of maintenance therapy, though inhaled corticosteroids (ICS) and long-acting β_2-agonists (LABAs) are preferred for long-term control.

Forms & Dosage

- **Inhalation (MDI/Nebulizer):** 250-500 mcg via inhaler every 4-6 hours as needed.
- **Oral Tablets:** 2.5-5 mg, 3 times daily.
- **Subcutaneous Injection:** 0.25 mg every 15-30 minutes in severe cases.

Advantages

✔ **Rapid onset of action (5-15 minutes)** – ideal for acute asthma attacks.

✔ **Less cardiovascular side effects** than older β_2-agonists like epinephrine.

✔ **Effective for exercise-induced bronchospasm**.

Side Effects & Precautions

 Common: Tremors, palpitations, headache, dizziness, nervousness.

 Severe: Tachycardia, arrhythmia, hypokalaemia (low potassium), paradoxical bronchospasm (rare).

 Caution in: Cardiovascular diseases, hyperthyroidism, diabetes, pregnancy (use only if benefits outweigh risks).

Comparison with Other SABAs

Table 1: Short acting beta agonists drugs.

Drug	Onset	Duration Form
Terbutaline	5-15 min	3-6 hours Oral, SC, Inhaler
Albuterol(Salbutamol)	5 min	4-6 hours Inhaler, Nebulizer
Levalbuterol	5-10 min	6-8 hours inhaler

 Key Difference: Terbutaline is also available in oral and subcutaneous forms, unlike most SABAs, making it an alternative in severe asthma when inhalation is not feasible.

Clinical Use & Guidelines

 Short-term relief: Recommended for acute exacerbations and EIB.

 Not for long-term control: Should not replace inhaled corticosteroids (ICS) or long-acting β_2-agonists (LABAs).

 Use with caution: Repeated or excessive use may lead to tolerance or reduced response over time.

Salmeterol

Salmeterol is a long-acting beta-2 adrenergic receptor agonist (LABA) widely used in the management of respiratory conditions such as asthma and chronic obstructive pulmonary disease (COPD). Its extended duration of action makes it particularly effective for long-term control of bronchoconstriction. Below is a comprehensive overview of salmeterol, encompassing its pharmacological properties, clinical efficacy, safety profile, and therapeutic applications.

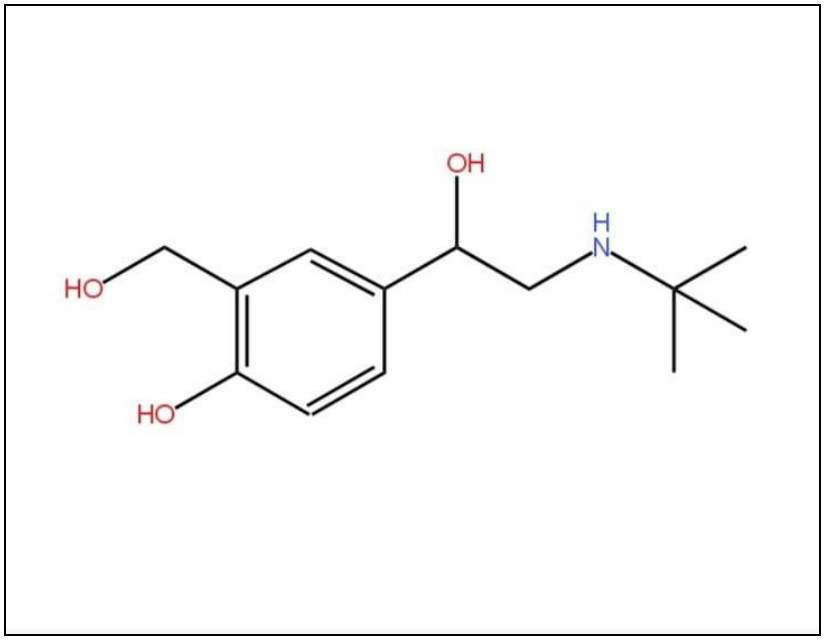

Fig. 2: Represents the structure of Salmeterol.

Pharmacological Properties

- **Mechanism of Action:** Salmeterol functions by selectively stimulating beta-2 adrenergic receptors located in the bronchial smooth muscle. This stimulation activates intracellular adenyl cyclase, catalyzing the conversion of adenosine triphosphate (ATP) to cyclic adenosine monophosphate (cAMP). Elevated cAMP levels lead to relaxation of bronchial smooth muscle, resulting in bronchodilation and improved airflow.

- **Duration of Action:** Unlike short-acting beta-2 agonists (SABAs) such as albuterol (salbutamol), which have a duration of 4–6 hours, salmeterol provides bronchodilation for approximately 12 hours. This extended effect is attributed to its high lipophilicity, allowing it to integrate into the lipid bilayer of cell membranes and provide a sustained release of the active compound.

Clinical Efficacy

- **Asthma Management:** Clinical trials have demonstrated that salmeterol, administered at 42 micrograms twice daily, significantly improves asthma-specific quality of life, controls asthma symptoms, and enhances pulmonary function in patients with mild-to-moderate persistent asthma. These improvements were maintained over a 12-week period.[25]

- **COPD Management:** In patients with COPD, the combination therapy of salmeterol and fluticasone propionate has been associated with improved lung function and quality of life. A notable study reported that the all-cause mortality rate over a three-year period was lower in the combination-therapy group (12.6%) compared to the placebo group (15.2%).[26]

Safety Profile

- **Monotherapy Risks:** The use of LABAs like salmeterol as monotherapy in asthma management has been associated with an increased risk of asthma-related adverse events. Therefore, current guidelines recommend that salmeterol should not be used alone but rather in combination with inhaled corticosteroids (ICS) to mitigate these risks.[27]
- **Combination Therapy:** Studies have shown that combining salmeterol with fluticasone propionate does not increase the risk of serious asthma-related events compared to fluticasone alone. This combination therapy is effective in improving asthma control and lung function while maintaining a safety profile comparable to ICS monotherapy.[28]

Therapeutic Applications

- **Asthma:** Salmeterol is indicated for the maintenance treatment of asthma in patients requiring regular bronchodilation. It is not intended for relief of acute bronchospasm.
- **COPD:** In COPD, salmeterol is used to improve symptoms and reduce exacerbations. Its long-acting bronchodilator effect helps in maintaining open airways, thereby enhancing breathing comfort.

CONCLUSION

The comparative study of **Terbutaline** and **Salmeterol** in the treatment of asthma reveals significant differences in their efficacy, mechanism of action, and appropriate clinical usage.

- **Terbutaline**, a short-acting beta-2 adrenergic agonist (SABA), is highly effective for **acute bronchospasm** and **exercise-induced bronchospasm (EIB)** due to its rapid onset of action (5-15 minutes) and shorter duration (3-6 hours). Its versatility, with forms including oral, subcutaneous, and inhalation, provides flexibility in emergency and non-inhalation cases. However, its effects are transient, making it less suitable for long-term asthma management.
- **Salmeterol**, a long-acting beta-2 adrenergic agonist (LABA), offers sustained bronchodilation for **12 hours**, making it ideal for **maintenance therapy** in asthma and **COPD**. Clinical trials have demonstrated its effectiveness in improving lung function and quality of life when combined with inhaled corticosteroids (ICS). However, it is unsuitable for acute asthma attacks and carries risks of asthma-related adverse events if used as monotherapy.

The study underscores that **Terbutaline** is best suited for **immediate symptom relief**, whereas **Salmeterol** is optimal for **long-term control** when used in combination with ICS. A tailored approach based on the patient's condition, frequency of exacerbations, and risk factors is essential for effective asthma management.

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