

Safety and Efficacy of Tiotropium Bromide in Bronchial Asthma Patients

Sridevi K¹, Mohana Rao V², Dr.G.Manoj Someswar³, Vijaya .N⁴

^{#1}Dept. of pharmacology, Rajiv Gandhi institute of Medical Sciences, Kadapa, AP., India.

^{#2}Dept. of Biochemistry & Molecular Biology, Institute of Genetics and Hospital for Genetic Diseases, Osmania University, Hyderabad, A.P., India.

^{#3}Senior Scientist, Monco Biotechnologies Pvt. Limited, Ameerpet, Hyderabad, A.P., India.

^{#4}Dept. of Pharmacology, Osmania Medical College, Hyderabad, AP., India

ABSTRACT: Bronchial Asthma is chronic inflammatory disorder of airways. It is characterized by airflow obstruction that is typically reversible and by airway hyper responsiveness to various stimuli. According to World Health Organization (WHO), between 100 and 150 million people around the globe suffer from Asthma and the number is rising (6). Worldwide deaths from this condition have reached over 1,80,000 annually. In case of Bronchial asthma, the gross histopathological studies show that the lungs are overdistended and there may be small areas of atelectasis. The most striking macroscopic finding is occlusion of bronchi and bronchioles by thick tenacious mucus plugs. Histologically, the mucus plugs contain whorls of shed epithelium which gives rise to the curschmann spirals. To overcome the above problem in this paper we introduced Tiotropium and demonstrated to provide superior safety and efficacy relative to placebo in both COPD as well as Br. Asthma group in both clinical assessment score and spirometrically. In the spirometric assessment with Tiotropium in COPD treatment group (n=48), reports showed significant improvement in FEV₁ i.e. 0.22L, in FVC 0.31L and FEV₁/FVC ratio was improved by 96% with respect to the baseline, which is statistically significant (P<0.001). These reports showed significant improvement with Tiotropium both clinically as well as spirometrically with fewer side effects i.e. mild dry mouth.

I. INTRODUCTION

Bronchial Asthma is chronic inflammatory disorder of airways. It is characterized by airflow obstruction that is typically reversible and by airway hyper responsiveness to various stimuli. According to World Health Organization (WHO), between 100 and 150 million people around the globe suffer from Asthma and the number is rising (6). Worldwide deaths from this condition have reached over 1,80,000 annually. India has an estimated 15-20 million asthmatics. It is estimated that 4-5% of population of US and 10-15% of UK population are affected with Asthma. The clinical development of Tiotropium has focused on its use as a long-acting bronchodilator in patients with Bronchial Asthma. Tiotropium bromide is a new quaternary ammonium compound with anticholinergic properties specific for muscarinic receptors (M1, M2 & M3) in humans (7). Because acetylcholine increases bronchial muscle tone, through vagal nerve stimulation and primarily M3 muscarinic receptors, acetylcholine blockade with anticholinergic medications may reduce bronchoconstriction and improve airflow.

While asthmatic patients with chronic bronchitis or emphysema may be included in these trials, but pure asthma patients are not the patients who have not been studied with this medication. Therefore, it is difficult to recommend this medication for regular use in asthmatics and impossible to recommend it as the “single bronchodilator” for the management of asthmatic patients. However, there is evidence that Tiotropium bromide improves airflow (FEV₁) and blocks the bronchoconstrictive effects of Methacholine in patients with Asthma (8). While Tiotropium bromide cannot be recommended as ‘bronchodilator of choice’ in patients with asthma, it provides measurable degree of bronchodilation and is well tolerated with no serious drug-related adverse effects. Hence the purpose of the present study was to evaluate the efficacy and safety of 18mcg Tiotropium metered dose inhalation, administered once daily for 14 weeks in patients Bronchial asthma, cross over study with placebo. Asthma prevalence in the United States is estimated at approximately 30 million based on the latest National Health and Nutrition Examination Survey III. Asthma and COPD are clinically defined airway disorders that individually have significant heterogeneity with regard to underlying pathogenesis and responses to therapy.

For both conditions, the chronic inflammation can lead to structural changes referred to as airway remodelling. These changes are believed to be irreversible and cause gradually worsening airflow obstruction

and reduced response to bronchodilators and glucocorticosteroids. Bronchodilators play a central role in symptomatic relief of acute bronchoconstriction in asthma patients. Asthmatics with any stage of persistent disease should be treated with inhaled glucocorticosteroids as their first line of control and maintenance, but the majority also benefit from use of a long-acting inhaled bronchodilator as part of their maintenance regimen.

The pathophysiologic hallmark of Asthma is a reduction in airway diameter brought about by contraction of smooth muscle, vascular congestion, edema of the bronchial wall and thick tenacious secretion. The net result is an increase in airway resistance, a decrease in forced expiratory volumes and flow rates, hyperinflation of the lung and thorax, increased work of breathing, alteration in respiratory muscle function, changes in elastic recoil, abnormal distribution of both ventilation and pulmonary blood flow with mismatched ratios and arterial blood gas concentration. In case of Bronchial asthma, the gross histopathological studies show that the lungs are overdistended and there may be small areas of atelectasis. The most striking macroscopic finding is occlusion of bronchi and bronchioles by thick tenacious mucus plugs. Histologically, the mucus plugs contain whorls of shed epithelium which gives rise to the curschmann spirals.

Numerous eosinophils and Charcot-Laden crystals are present, which are collections of crystalloids made up of eosinophils membrane protein. The other characteristic histological findings of asthma include.

- a. Thickening of the basement membrane of the bronchial epithelium.
- b. Edema and an inflammatory infiltrate in the bronchial walls, with a prominence of eosinophil's which form 5 to 50% of the cellular infiltrate.
- c. Hypertrophy of bronchial wall muscle a reflection of prolonged bronchoconstriction.
- d. An increase in the size of mucosal glands.

Etiopathogenesis Of Bronchial Asthma

1. **Environment and air Pollution:**-Ozone, Nitrogen dioxide and Sulphur dioxide tend to aggravate asthma.
2. **Occupational factor:** - Bronchoconstriction can result from working with or being exposed to metal salts like platinum, chromium and nickel, wood and vegetable dust, pharmaceutical agents like antibiotics, cimetidine and piperazine, industrial chemicals and plastics, animals and insect dusts and serum and secretions.
3. **Infections:** - Respiratory infections are the most common stimuli that evoke acute exacerbations of Asthma. In young children, the most important infectious agents are respiratory syncytial virus and parainfluenza virus. In older children and adults rhinovirus and influenza virus predominate as pathogens.
4. **Allergens:**-Most of the allergens that promote asthma are airborne. Allergic asthma is airborne. Allergic asthma is frequently seasonal and it is most often observed in children and young adults. A non seasonal form may result from allergy to feathers, animal dander, dust mites, moulds and other antigens that are present continuously in the environment.
5. **Genetic factors:** -Asthma has strong familial component. Evidence for genetic linkage of high total serum immunoglobulin E (IgE) levels and atopy has been observed on chromosomes 5q, 11q, and 12q (22).
6. **Pharmacological stimuli:** -The drugs most commonly associated with the induction of acute episodes of asthma is aspirin, other NSAIDS, B-adrenergic receptor antagonists, colouring agents such as tartrazine, and agents such as potassium and sodium bisulphate which are widely used in food and pharmaceutical industries as sanitizing and preserving agents.
7. **Emotional Stress:** -Emotional stress can evoke acute exacerbation of asthma, changes in airway caliber seem to be mediated through modification of vagal efferent activity. Endorphins may also play a role.
8. **Exercise:** -Exercise is a very common precipitant of acute episodes of asthma. It does not evoke any long-term sequelae nor does it increase airway reactivity. Airway obstruction occurs due to thermally produced hyperemia and engorgement of microvasculature of bronchial wall. It does not appear to invoke smooth muscle contraction

II. RELATED WORK

Classification of Asthma:

Asthma is broadly classified into two types---

1. Extrinsic asthma.
2. Intrinsic asthma.

Extrinsic asthma:-This begins usually in childhood. The disease is triggered by environmental antigens such as pollens, dusts and food but potentially any antigen is implicated. A positive family history of atopy is common,

serum IgE levels are elevated and asthmatic attacks are often preceded by allergic rhinitis, urticaria and eczema.

Intrinsic asthma:-This is initiated by diverse non immune mechanisms including ingestion of aspirin, pulmonary infections, inhaled irritants, exercise and stress. A positive family history is uncommon. Serum IgE levels are normal.

Drug induced asthma:- Several pharmacological agents like aspirin and ibuprofen provoke asthma. Aspirin sensitive asthma occurs in patients with recurrent rhinitis and nasal polyps. These individuals are extremely sensitive to small dose of aspirin. It is probable that aspirin triggers asthma in these patients by inhibiting the cyclo-oxygenase pathway of arachidonic acid metabolism without affecting the lipooxygenase route, there by producing bronchoconstriction by leukotrienes. Patients manifest overlapping characteristics e.g. the patient with extrinsic asthma is also more likely to manifest bronchospasm after exposure to one of the agents associated with intrinsic asthma and vice versa(24). So this classification is used with diminishing frequency because it lacks sufficient discriminating power to aid in establishing an etiologic diagnosis or to help in defining treatment strategies.

Clinical Features: Wheezing occurs frequently, but often is attributed to asthma or a viral respiratory tract infection leading to diagnosis of Asthma. In 1995, the American Thoracic Society stated "It may be impossible to differ differentiate patients with Asthma whose airflow obstruction does not completely from patients with chronic bronchitis and emphysema with partially reversible air flow obstruction and bronchial hypersensitivity⁽²⁵⁾. More recently current Asthma guidelines⁽²⁶⁾ have emphasized that there may be fixed or irreversible component to airway obstruction in some patients with asthma. Asthma is characterized by episodic wheezing, dyspnea and cough. At the onset of an attack, patients experience a sense of contraction in the chest often with a non-productive cough. Patients will have frequently tachypnea, tachycardia and mild systolic hypertension. If the attack is severe, there may be loss of adventitial breath sounds and wheezing becomes very high pitched. The accessory muscles become visibly active, and a paradoxical pulse often develops. These two signs are extremely valuable in indicating the severity marked by a cough that produces thick, stringy mucus which often takes the form of casts of distal airways (Curschmann spirals) and when examined microscopically often shows eosinophils and Charcot-Laden crystals.

Drug Review: A major advance in COPD therapy was the development of Tiotropium bromide that could be delivered to the lungs via inhalation. This drug is also effective for the patients of asthma. This allowed for the targeting of the drug directly to the relevant site of inflammation. The therapeutic index of the drugs has been gently enhanced by substantially diminishing the number and degree of side effects without sacrificing clinical efficacy.

III. TIOTROPIUM BROMIDE

Tiotropium bromide is long acting, specific, muscarinic receptor antagonist, in clinical medicine often called an anticholinergic. By binding to the muscarinic receptors in the bronchial smooth musculature, Tiotropium bromide inhibits the cholinergic effects of acetylcholine, released from parasympathetic nerve endings. The long duration is probably due to the very slow dissociation from the M₃ receptor, exhibiting a significantly longer dissociation half life than ipratropium. It is chemically described as 1(alpha),2(beta),4(beta),5(alpha)& 7(beta),7[c-hydroxyde-2-thienylacetyl]oxy]-9,9-dimethyl-3-oxa-9-azoniatricyclo(3.3.1.0^(2,4))Nonanebromide mono-hydrate. It is a synthetic, non-chiral, quaternary ammonium compound. Tiotropium bromide is a white or yellowish white powder. It is sparingly soluble in water and soluble in methanol. (Fig-3). Tiotropium bromide (monohydrate) has a molecular mass of 490.4 and a molecular formula of C₁₉ H₂₂ NO₄ S₂ Br H₂O. As Tiotropium bromide is quaternary ammonium compound with a charge at the 5-valent nitrogen atom that renders it water and lipid insoluble, and consequently this drug has much lower systemic absorption. Thus, this synthetic compound has much less potential for causing side effects, even at levels much higher than recommended doses.

Pharmacokinetics:

Tiotropium is administered by dry powder inhalation. In common with other inhaled drugs, the majority of the delivered dose is deposited in gastrointestinal tract and to a lesser extent, in the lung, the intended organ. Tiotropium causes a relatively slower improvement in FEV₁ but reaches a peak between 1 and 3 h and is sustained for >24 h owing to its very long dissociation half-life of >34 hr.

- a. **Absorption:** - Following dry powder inhalation by young healthy volunteers, the absolute bioavailability of 19.5%. It is expected from the chemical structure of the compound (quaternary ammonium

- compound) that Tiotropium is poorly absorbed from GI tract. Food does interfere with the absorption of the Tiotropium. Maximum Tiotropium plasma concentrations were observed 5 min after inhalation.
- b. **Distribution:**- Tiotropium shows a volume of distribution of 32 L/kg indicating that the drug binds extensively to tissue. The drug is bound by 72 % to plasma proteins. At steady state, peak plasma levels in COPD patients were 17-19 pg/ml when measured 5min after dry powder inhalation of an 18mcg dose and decreased rapidly in multicompartmental manner. Steady state trough plasma concentration was 3-4 pg/ml. Studies in rats have shown that Tiotropium does not readily penetrate the blood-brain barrier.
 - c. **Bio Transformation:** - The extent of this is appears to be small. This is evident from a urinary excretion of 74% of unchanged substance after an intravenous dose to young healthy volunteers. Tiotropium an ester is non-enzymatically cleaved to the alcohol N-methylscopine and dithienylglycolic acid, neither of which bind to muscarinic receptors. In vitro experiments with human liver microsomes and human hepatocytes suggests that a fraction of the administered dose (74% of an intravenous dose is excreted unchanged in the urine, leaving 25% for metabolism) is metabolized by cytochrome P₄₅₀-dependent oxidation and subsequent glutathione conjugation to a variety of phase-II metabolites. This enzyme pathway can be inhibited by CYP₄₅₀ 2D₆ and 3A₄ inhibitors such as quinidine and ketoconazole. Thus CYP₄₅₀ 2D₆ and 3A₄ are involved in the metabolic pathway that is responsible for the elimination of a small part of administered dose.
 - d. **Elimination:** - The terminal elimination half life of Tiotropium is between 5 and 6 days following inhalation. Total clearance was 880 ml/min after an intravenous dose in young healthy volunteers with an inter-individuals variability of 22%. IV administered Tiotropium is mainly excreted unchanged in urine (74%). After dry powder inhalation, urinary excretion is 14% of the dose, the remainder being mainly non-absorbed drug in the gut which is eliminated via faeces. The renal clearance of Tiotropium exceeds the creatinine clearance, indicating active secretion into the urine. After chronic once daily inhalation by COPD patients pharmacokinetic steady state was reached after 2-3 weeks with no accumulation thereafter.

Mechanism of Action:

Tiotropium is a long acting anticholinergic agent. It has similar affinity to the subtypes of muscarinic receptors M₁ to M₅. In the airways, it exhibits pharmacological effects through inhibition of M₃ receptors at the smooth muscle leading to bronchodilation. The competitive and reversible nature of antagonism was shown with human and animal origin receptors and isolated organ preparations. In pre-clinical in vitro as well as in vivo studies prevention of methacholine induced bronchoconstriction effects were dose dependent and lasted longer than 24 hrs. The bronchodilation following inhalation of Tiotropium is predominantly a site-specific effect. The submucosa of human airways both upper and lower contain afferent irritant receptors and nociceptive C fibers that can be triggered to fire by a wide assortment of stimuli including many irritant gases i.e. cigarette smoke aerosols particles, cold dry air, mechanical irritation and various specific mediators. Once stimulated the C fibers transfer the impulse through vagal afferents up to vagal nuclei in the brainstem and then down through vagal efferents to the larger airways that receive vagal innervations.

Parasympathetic cholinergic efferents supply most of the autonomic innervation to the human airways. They synapse in peribronchial ganglia with short postganglionic nerves that have muscarinic-1 (M₁) receptors. These neurons in turn release acetylcholine that stimulates muscarinic-3 (M₃) receptors found on smooth muscle and submucosal glands. This leads to bronchoconstriction and mucus gland secretion and increased ciliary beat frequency. This reflex are likely contributes to bronchospastic events that asthmatic patients experience when exposed to various environmental triggers. Muscarinic-2 (M₂) receptors are located on the distal terminus of the short postganglionic fibers and have an autoreceptor function of feedback inhibition to shut down acetylcholine release from post ganglionic fibers. These receptors play an important role in down regulating the release of acetylcholine in the synapses with M₃ receptors on smooth muscle and consequently limit the amount of bronchoconstriction. There is also evidence to suggest that basal cholinergic tone is increased in asthma leading to tonic relative bronchoconstriction that contributes to the chronic persistent airflow limitation found in these disorders.

Anticholinergic agents compete with acetylcholine for these various muscarinic receptors and block bronchoconstriction and mucous gland secretion. Because cholinergic stimulation is only one of many contributing factors leading to bronchoconstriction, anticholinergics can only partially reverse the airflow obstruction of asthma. Furthermore, as outlined above, anticholinergic blockade of the M₂ receptors may actually promote further bronchoconstriction because of their feedback inhibition role. Unfortunately, most anticholinergic agents have no selectivity when it comes to stimulating M₁, M₂, or M₃ receptors. Tiotropium, a congener of ipratropium bromide, has been reported to bind avidly to M₁ and M₃ receptors while dissociating

rapidly from M₂ receptors, thus having a relative selectivity that promotes bronchodilation. The anticholinergic agents can partially reverse the bronchoconstriction that occurs in asthma and COPD, but they have no or minimal known effect on leukotrienes and other components or mechanisms of airway inflammation. For these reasons, their greatest role and indication has been as a primary bronchodilator in the treatment of COPD. Moreover, from the above discussion it is evident that there are reasonable grounds to consider that anticholinergic agents may have some role complementary to β -agonists in the treatment of at least a subset of patients with asthma and COPD.

Dose and administration:

- 18 mcg /once daily in the morning by inhalation with Rotahaler device.
- The recommended dose should not be exceeded.
- Tiotropium bromide rotacaps must not be swallowed.

Drug interactions: Although no formal drug interaction studies have been performed, Tiotropium bromide inhalation powder has been used concomitantly with other drugs without adverse drug reactions. These include sympathomimetic bronchodilators, methylxanthines, oral and inhaled steroids commonly used in the treatment of COPD. Only one study of interaction with Tiotropium with cimetidine 400 mg three times daily or ranitidine 300mg once daily was conducted, which showed no clinically significant interactions occurred between Tiotropium and cimetidine or ranitidine.

Contraindications: -Tiotropium bromide inhalation powder is contraindicated in patients with hypersensitivity to Tiotropium bromide, atropine or its derivatives eg ipratropium or oxitropium or to the excipient lactose monohydrate.

Adverse Reactions: - Several organ system and functions are under control of the parasympathetic nervous system and thus can be affected by anticholinergic agents. Possible adverse effects attributable to systemic anticholinergic effects include- dry mouth, dry throat, increased heart rate, blurred vision, glaucoma, urinary retention and constipation. In addition, local upper airway irritant phenomena were observed in patients receiving Tiotropium bromide. An increased incidence of dry mouth and constipation may occur with increasing age. The most common anticholinergic adverse reaction reported by COPD patients was dry mouth, which was mild in the majority of cases.

Warnings and precautions:-

Tiotropium bromide should not be used for the initial treatment of acute episodes of bronchoconstriction i.e. rescue therapy. As with other anticholinergic drugs, Tiotropium bromide should be used with caution in patients with narrow-angle glaucoma, prostatic hyperplasia, bladder-neck obstruction. Inhaled medicines may cause inhalation induced bronchospasm. The drug should be used cautiously in renal and hepatic failure patients. Patients should avoid getting the drug powder into their eyes. They should be advised that this may result in precipitation a worsening of narrow angle glaucoma, eye pain or discomfort, temporary blurring of vision, visual haloes or colored images in association with red eyes from conjunctival or corneal congestion. Even though no clinical studies were available about the effect in pregnant and lactating mothers, but the animal studies have shown reproductive toxicity associated with maternal toxicity. Therefore Tiotropium bromide should not be used in pregnant or nursing women. Tiotropium bromide should not be used for cardiac or susceptible patient as it may produce supraventricular tachycardia and atrial fibrillation as cases were reported in coronary artery disease patients.

Over dose:-High doses of Tiotropium bromide may lead to anticholinergic signs and symptoms. However, there were no systemic anticholinergic adverse effects following a single inhaled dose of up to 340 mcg Tiotropium bromide in healthy volunteers. Additionally, no relevant adverse effects beyond dry mouth were observed following 7-days dosing of up to 170 mcg of Tiotropium bromide in healthy volunteers. Acute intoxication by inadvertent oral ingestion of Tiotropium bromide capsule is unlikely due to low oral bioavailability.

Salbutamol :-It is a selective beta₂ adrenergic receptor agonist. It is chemically alpha-1-[(tert-butylamino) methyl-] -4- hydroxyl -m- xylene- alpha -alpha-diol. Its empirical formula is C₁₃ H₂₁ NO₃. It is a white crystalline powder sparingly soluble in water and freely soluble in ethanol.

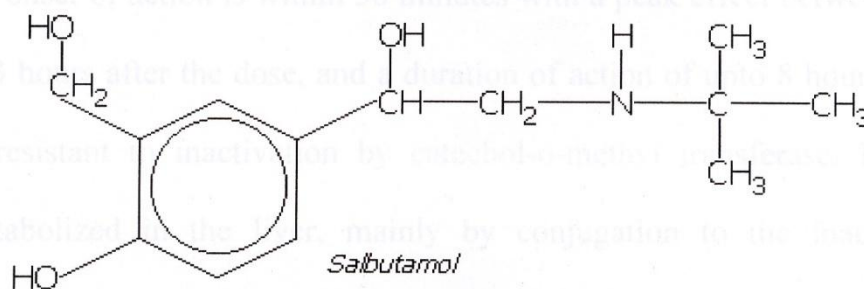


Fig.1. chemical structure of Salbutamol

Pharmacokinetics:-Salbutamol can be given orally, parenterally and also by inhalation. It is readily absorbed from gastro-intestinal tract. Following inhalation, the onset of action is within 5 to 15 minutes and lasts for about 3 to 6 hours. Following administration by mouth the onset of action is within 30 minutes with peak effect between 2 to 3 hours after the dose and duration of action is 8 hours. It is resistant to inactivation by catechol-o-methyl transferase. It is metabolized in the liver, mainly by conjugation to the inactive salbutamol-4-O-sulphate. Its plasma half life is 2.7 to 5 hrs after oral administration. It is 3.8 hours after inhalation. 72 % of the unchanged drug and metabolite are excreted in the urine within the first 24 hrs.

Dose: - Inhalation – 100 mcg 4 times daily. Oral - 2 mg , 3 times daily.

Adverse Effects:-Salbutamol may cause fine tremors of skeletal muscle (particularly the hands), palpitations, tachycardia, nervousness, headaches, peripheral vasodilatation. Hypersensitivity reaction including paradoxical bronchospasm, angioedema, urticaria. Hypotension can occur rarely. Hypokalaemia has been reported with high doses. Inhalation causes fewer side effects than systemic administration.

Drug Interaction:-Concomitant administration of high doses of salbutamol with corticosteroid, diuretics, or xanthine increases the risk of hypokalaemia. When given intravenously it has been reported to enhance the neuromuscular blockade produced by pancuronium and by vecuronium. No drug interactions are noted with inhalation form.

IV. EXPERIMENTS

Materials And Methods

The present clinical study was conducted in patients with stable as well as exacerbated COPD and Bronchial asthma in Andhra Pradesh Government General and chest Hospital from May 2005 to Feb 2006. A total of 120 patients, out of which 50 patients with mild to moderate COPD, 50 Bronchial asthma patients and another 20 patients each 10 with placebo study. They were diagnosed based on the clinical findings and pulmonary function tests. The study was conducted for a period of 14 weeks.

Study Design

This is an open label, randomized, parallel group study. The total number of patients in both COPD and Bronchial Asthma categories were randomized into 3 groups; had 50 patients bronchial asthma, 50 patients of COPD and 20 patients each disease with placebo.

Group I received - 50 patients of COPD.

Treated with 18mcg of Tiotropium. (2puffs/day)

Group II received - 50 patients of Bronchial Asthma.

Treated with 18mcg of Tiotropium inhaler. (2puffs/day)

Group III – Group-III A, 10 patients of COPD and Group-III B, 10 Bronchial asthma patients

Both groups received, Inhalation with placebo

2 puffs / day , everyday morning

Inclusion Criteria for Bronchial Asthma Patients:-

Patients with the following criteria were included in this study:-

1. Patients in the age group of 12 to 65 yrs of either sex.
2. Patients with the history of episodic wheezing, difficulty in breathing, chest tightness, and cough with or without expectoration.

3. Patients having nocturnal symptoms and family history of asthma.
4. Patients with the history of seasonal and the diurnal variation.
5. Patients with the history of non-smokers.

Inclusion Criteria for COPD Patients:-

1. Patients in the age group of 40 to 70 of either sex.
2. Patients with the history of cough, productive sputum and SOB.
3. Patients with the history of smoking, 10 packs / year or more, FEV₁ of 65 % or less of predict for age.
4. Patients must be willing to give written informed consent and able to adhere to dose and visit schedule.
5. Patients who are stable on inhaled corticosteroids are allowed to be enrolled and to remain on the treatment throughout the study.

Investigations:-

The following investigations were done:-

- 1) Blood Examination:-
 - (a) Haemoglobin
 - (b) Total count
 - (c) Differential count
 - (d) Absolute eosinophiles count
 - (e) Erythrocyte sedimentation Rate
 - (f) Peripheral smear
 - (g) Random Blood Sugar
 - (h) Serum Creatinine
- 2) Sputum Examination:-
 - a) Eosinophilic Count.
 - b) A.F.B.
- 3) Electrocardiography.
- 4) Chest x-ray PA view.
- 5) Pulmonary function test.

(Baseline, after drug administration, 5 times in the 1st day, 3rd day, 7th day and every 2nd week up to three and half months).Blood examination, Sputum examination, chest x-ray, ECG were done to exclude other Conditions,A written informed consent was obtained from the patient.

Patient was given study number and included in one of the group:-

Group I: - COPD patients-(50 cases).

Drug - Tiotropium bromide inhalation.

Dose - 18 mcg, once daily.

Duration - 14 weeks.

Group. II: - Br. Asthma Patients. (50 cases).

Drug - Tiotropium bromide inhalation.

Dose – 18 mcg. Once daily.

Duration – 14 weeks.

GroupIII:- GpIIIA : COPD patients treated with placebo, GpIIIB: Bronchial asthma patients treatedwith placebo,Either cases (10 each).

Drug – Placebo.

Dose – 2 puffs / day.

Duration: - 14 weeks.

All the patients were advised to take salbutamol inhalation (100-150 mcg) as needed. All the drugs were given as metered dose inhalation. Patients were shown inhalation techniques with spacers. They were advised to rinse their mouth after each inhalation. They were followed up 3 times in the 1st week after that every 2nd week till a period of 14 weeks. At each visit, they were clinically assessed and PFT was done.

Screening was done for the following parameters before and after treatment:-

- 1) Cough
- 2) Wheeze
- 3) Breathlessness
- 4) Severity of nocturnal symptoms
- 5) Frequency of use of rescue Medication.

Score for Cough, Wheeze, Breathlessness and Severity of nocturnal Symptoms⁽³³⁾ for Br. Asthma:-

- 0 - No Symptoms
 1 - Mild
 2 - Moderate
 3 - Severe

Score for frequency of Use of Rescue Medication ⁽³⁴⁾

- 0 - < 2 puffs / week.
 1 - < 2 Puffs day.
 2 - 2 to 4 Puffs /day.
 3 - > 4 Puff / day.

At each visit, patients were assessed for any adverse effects. Hence the diagnosis of COPD can be confirmed with the help of spirometry. The differences between COPD and Asthma have an important bearing on treatment.

COPD: - Backbone of treatment inhaled bronchodilators.

Asthma: - Backbone of treatment inhaled corticosteroids.

V. RESULTS AND CONCLUSION

The Present study showed Tiotropium was demonstrated to provide superior safety and efficacy relative to placebo in both COPD as well as Br. Asthma group in both clinical assessment score and spirometrically. In the spirometric assessment with Tiotropium in COPD treatment group (n-48), reports showed significant improvement in FEV₁ i.e. 0.22L, in FVC 0.31L and FEV₁/FVC ratio was improved by 96% with respect to the baseline, which is statistically significant (P<0.001). Clinically symptomatic improvement was observed in cough, SOB, wheeze and nocturnal severity of symptoms. Frequency of rescue medication was also decreased by mean change score of 0.45(78.2%) with regard to baseline score 2.10(P<0.001) during the period of 14 weeks. In case of Bronchial asthma treatment group (n-50) reports showed significant improvement in both clinically as well as spirometrically but less effective compared with COPD treatment group. In spirometric assessment, FEV₁ is improved by 0.21L, FVC by 0.31L and FEV₁/FVC ratio improved by 92.14% with respect to baseline which is statistically significant (P<0.005). Clinically, the mean score reports showed 60-70% improvement when compared to baseline. These reports showed significant improvement with Tiotropium both clinically as well as spirometrically with fewer side effects i.e. mild dry mouth. Many studies are available with Tiotropium in COPD patients, which provides consistent reports of efficacy and safety of this drug but very few studies are available with Tiotropium in Bronchial asthma patients. However, it will be important to perform further comparative studies with large sample in multi centric studies, using Tiotropium in all the stages of Bronchial asthma patients to evaluate the safety and efficacy of the drug and also to document the role of Tiotropium in Bronchial asthma. In spirometric as well as clinically, placebo in COPD group patients (n-7) and Bronchial asthma group patients (n-10) showed very less improvement, which is statistically not significant. The improvement observed was superior to placebo 2puff/day with MDI. The over all results of our study suggests that Tiotropium in the dose of 18 mcg once daily via dry powder inhaler result in 24 hr bronchodilation as well as consistent and sustained improvement for both the COPD and the Bronchial asthma patients. It is safe and efficacious drug both clinically and spirometrically. Our study showed decrease in symptoms, decrease in rescue medication frequency and also reduce frequency of acute attacks.

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Author 1. Dr.K.Sridevi , M.B.B.S., M.D.,Working as Associate Professor in the Dept of Pharmacology, Rajiv Gandhi Institute of Medical Sciences(RIMS), Kadapa, A.P., India.

Author 2. Dr. Mohana Rao Vayalapaty PhD,PDF(USA), Dept. of Biochemistry & Molecular Biology, Institute of Genetics and Hospital for Genetic Diseases, Osmania University, Hyderabad, A.P., India.



Author 3. Dr.G.Manoj Someswar, Ph.D. He is a Senior Scientist in Monco Biotechnologies Pvt. Ltd., Ameerpet, Hyderabad-500016, A..P., India.



Author 4. Dr.N.Vijaya, M.B.B.S., M.D. She is working as Professor of Pharmacology, Osmania Medical College, Hyderabad, A.P., India.