Safety and Efficacy of Tiotropium Bromide in Copd Patients

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Abstract- Chronic obstructive pulmonary diseases (COPD) are a potentially fatal, slowly progressive respiratory disease. In contrast to Asthma, COPD is characterized by air flow obstruction that is not fully reversible. The signs and symptoms are chronic cough, excessive mucus production, wheezing and shortness of breath after mild exertion. In the USA, COPD affects more than 15 million people, with the majority of the patients being over the age of 50 years and current or past smokers. According to the World Health Organization (WHO) about 600 million people suffer from COPD although many are undiagnosed.

Index Terms- COPD, muscarinic receptors, anticholinergic, bronchoconstriction, hypoxemia, hypoventilation

I. INTRODUCTION

Chronic obstructive pulmonary diseases (COPD) are a potentially fatal, slowly progressive respiratory disease. In contrast to Asthma, COPD is characterized by air flow obstruction that is not fully reversible. The signs and symptoms are chronic cough, excessive mucus production, wheezing and shortness of breath after mild exertion. In the USA, COPD affects more than 15 million people, with the majority of the patients being over the age of 50 years and current or past smokers. According to the World Health Organization (WHO) about 600 million people suffer from COPD although many are undiagnosed.In practice, COPD tends to be under diagnosed and undertreated, for a number of reasons. However, the availability of detailed and practical guidelines from the Global Initiative for chronic obstructive Lung Disease (GOLD) will be useful for improving COPD care through primary care needs to respond by developing systems to ensure these guidelines are implemented in practice.There is no cure for COPD, and treatment is aimed mainly at controlling symptoms. Inhaled anticholinergic bronchodilators are now considered to be the first line treatment for COPD and exert their pharmacologic action by blocking muscarinic receptors, particularly M3 receptors.Tiotropium bromide, long acting, inhaled anticholinergic bronchodilator, which selectively inhibits the muscarinic receptors involved in mucus secretion and bronchoconstriction. Long term clinical trials have demonstrated the efficacy of Tiotropium in patients with COPD. Tiotropium bromide is a new quaternary ammonium compound with anticholinergic properties specific for muscarinic receptors (M1, M2 &M3) in humans (7).

The primary studies available for Tiotropium bromide enrolled patients older than 40yrs of age with a diagnosis of COPD, at least 10 packs /year of tobacco use and FEV1/FVC ratio <0.70 with FEV1<65% of predicted value. 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 with COPD and Bronchial asthma, cross over study with placebo. Asthma prevalence in the United States is estimated at approximately 30 million, and COPD prevalence may be as high as 24 million based on the latest National Health and Nutrition Examination Survey III. COPD is clinically defined as airway disorders that individually have significant heterogeneity with regard to underlying pathogenesis and responses to therapy.

In COPD 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 both conditions and are the primary maintenance therapy for COPD 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. Chronic obstructive pulmonary disease (COPD) is characterized by the progressive development of airflow limitation that is not fully reversible (9). There is some epidemiologic evidence that mucus hypersecretion is accompanied by airflow obstruction, perhaps as a result of obstruction of particularly peripheral airway (10).

The primary physiological abnormality in COPD is an accelerated decline in the forced expiratory volume in one second (FEV1) from the normal rate in adults over 40years of age of approximately 30ml per year to nearly 60ml per year (11). Hyperinflation which occurs at rest and worsens with exercise is commonly seen in patients with moderate to severe COPD. It is manifested primarily by an increase in the functional residual capacity which places the muscle of respiration at a mechanical disadvantage, thereby increasing the work of breathing and reducing exercise tolerance.

Additional physiological abnormalities include a reduction in the diffusing capacity to carbon monoxide, hypoxemia and hypoventilation. Epidemiology: - It is estimated that approximately 14 million people in the United States have COPD. In the 3rd U.S. National Health and Nutrition

examination survey, airflow obstruction was found in approximately 14% of white male smokers as compared with approximately 3% of white male non smokers; The figures for white female smokers and for black smokers were slightly lower than those for white male smokers (12). The World Health Organization predicts that by 2020 COPD will rise from its current ranking as 12th most prevalent disease worldwide to the 5th and from the 6th most common cause of death to the 3rd (13).

II. PATHOGENESIS OF COPD

The recognition of chronic airway inflammation has a critical role in producing the symptoms of asthma. It is now apparent that there is a chronic inflammatory process in COPD, but it differs markedly from that seen in asthma, with different inflammatory cells mediators, inflammatory effects and responses to treatment.(17) The basic pathophysiologic process in COPD consists of (fig-1) :-

1. Increased mucus production and reduced mucociliary clearance leading to cough and sputum production.
2. Increased smooth muscle contraction and leading to expiratory airflow limitation and classical symptoms of dyspnea.
3. Loss of elastic recoil leading to gas exchange abnormalities producing hypercapnia.

Bronchial biopsy results are similar to the histopathological findings:-

1. Patients with severe COPD have infiltration of macrophages and CD 8 + T cells and an increased number of neutrophils (20) .
2. There is a marked increase in macrophage and neutrophil in bronchoalveolar- lavage fluid and induced sputum (21) .
3. In patients with asthma, eosinophils are not prominent except during exacerbations or in patients with concomitant COPD (22)

Classification of COPD based on spirometry by ATS/ERS guidelines

Severity	Post bronchodilator FEV_1/FVC	FEV_1 % Predicted.
At risk	> 0.7	> / = 80.
Mild COPD		> /= 80.
Moderate COPD		50-80
Severe COPD		30-50
Very Severe COPD		< 30

III. CLINICAL FEATURES

Symptoms of COPD are progressive, beginning with mild dyspnea and occasional cough, followed by chronic productive cough with clear colourless sputum. COPD causes the walls of the small airways to thicken and the alveoli to lose their elasticity.

Many older individuals experience dyspnea on exertion because of deconditioning and obesity. Cough and sputum production is so common in smokers that it may be considered normal. The clinically silent nature of early COPD and the indolent course of the disease allows patients to accommodate their growing disability with life style changes. In the past, COPD has been defined in terms of in reversible airway obstruction that is progressive over time, but more recently the fact that patterns of COPD overlap with those of Asthma has been recognized. 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).]

The use of phenotypic characteristics (e.g. symptoms, allergy and bronchial hyperresponsiveness) may be useful to differentiate disease characteristics as well as help in understanding the similarities in the development and progression of both obstructive airway diseases. As Asthma and COPD share many common origins i.e. epidemiological characteristics and clinical manifestations, conclusions were based on a comparison of signs, laboratory findings, treatment responses and natural history.

Characteristics of Asthma and COPD

COPD
Progressive airflow obstruction.
smaller corticosteroid response
Cellular infiltration including neutrophils, macrophages,
Cytokine, chemokines and protease responses.

IV. DIFFERENTIAL DIAGNOSIS

In adults, the differential diagnosis of COPD includes –

1. **Asthma:** - The clinical features of COPD mostly mimic that of asthma. But the predominant clinical feature in asthma is episodic dyspnea and cough.

The typical physiological feature is variable airflow obstruction, and airway hyper reactivity is typical. The classic pathologic feature in asthma is airway inflammation, subepithelial basement membrane fibrosis, which is the diagnostic.

2**. Emphysema:** - The clinical and physiological features mimic that of the COPD but in emphysema the classic pathological feature is permanent abnormal enlargement of air spaces and destruction of alveolar wall.

3. **Chronic bronchitis:** - In this disease, the signs and symptoms are very much similar to that of the COPD but it can be differentiated it from COPD but based on the pathologic picture i.e. presence of mucus gland enlargement and airway smooth muscle hypertrophy.

Diagnosis: - In case of COPD, the majority of cases occur in patient who are smokers [27] . All current or former smokers should be considered at increased risk for COPD. Other risk factors which account for fewer cases include Alfa-1 antitrypsin deficiency, airway hyperresponsiveness [28] and indoor air pollution. Since symptoms may not occur until lung function is substantially reduced, early detection is enhanced by spirometric evaluation of FEV_1 and forced vital capacity (FVC). Guidelines from Global initiative for chronic obstructive Lung Disease (GOLD) state that the airflow limitation in COPD is characterized by an FEV_1 value that is less than 80% of the predicted normal value and FEV_1:FVC ratio of less than 0.70[29]. There is responsiveness to be a bronchodilator in 23 to 42 percent of patients with COPD, depending on criteria used. Furthermore, data from the Lung Health Study indicate that 59 percent of men and 85 percent of woman with moderate disease (mean (±SD) FEV_1: FVC ratio, 0.630±.055percent) have airway hyperresponsiveness.

Thus, although guideline-based spirometric criteria are useful starting points, differentiation of COPD from asthma requires careful integration of epidemiologic risk factors (including the patient's age, smoking status and family history), clinical status (including both the indolent and progressive nature of symptoms) and a knowledge of the distribution and potential overlap of physiological disturbances.

Treatment: -The major goals of COPD therapy include smoking cessation, symptoms relief, improvement in physiological function and limitation of complications, such as abnormal gas exchange and exacerbation of the disease. An integrated approach to treatment combines health care maintenance and use of drug and supplemental therapy is a step wise fashion as the disease progresses .The goals of asthma therapy are to minimise chronic symptoms that impair normal activity, to prevent recurrent exacerbation, to minimise the need for emergency department visits and maintain near normal pulmonary function. Treatment algorithms are based on both the severity of the patient's baseline asthma and the severity of asthma exacerbations. Expert panel report 2 from the NAEPP recommends a stepwise approach to therapy. Therapy should be initiated early at a higher intensity level than anticipated for chronic therapy. Pharmacotherapy can then be cautiously stepped down once asthma control is achieved and sustained. This allows for identification of the minimum medication necessary to maintain long-term control.

The measure of Health care maintenance in COPD consists of:-

(1). **Regular Assessment of Lung function:-** The spirometry may be performed in all patients at risk to detect asymptomatic airflow limitation. In patients with established disease spirometry should be performed at least annually and more frequently if needed, to assess clinical status or the response to therapy.

(2**). Smoking Cessation**:-Abstinence from smoking (Drug bupropion, a noradrenergic antidepressant used for smoking cessation) results in a sustained 50% reduction in the rate of lung function decline in patients with COPD and smoking cessation is the only intervention known to be effective in modifying the disease. Nicotine-replacement therapy (by gums, transdermal patch or inhaler) provides help to patients in quitting smoking.

(3). **Vaccination:-**Although there is little evidence of a direct benefit of vaccination in patients with COPD, but the pneumococcal vaccination and annual influenza vaccination be offered to all patients in an attempt to reduce both disease-specific mortality and mortality from all causes[30] . Drugs used in the treatment of COPD, as well bronchial asthma can be classified as bronchodilators and anti-inflammatory drugs.

(1). **Bronchodilators**:-

(A). $Beta_2$ adrenergic receptor agonists-

I. Short activity: Salbutamol, terbutaline, adrenaline, ephedrine.

II Long activity: Salmeterol, formoterol.

(B). Phosphodiesterase inhibitors: Theophylline,Aminophylline.

(C).Anticholinergics: Ipratropium bromide, Tiotropium bromide.

(2). Anti-inflammatory drugs:-

(A). Glucocorticoids:

I. Systemic: Prednisolone.

II. Inhalation: Beclomethasone dipropionate, Budesonide, Flunisolide, fluticasone propionate.

(3) Leukotriene [LT] modifiers:-

I. LT synthesis inhibitors- zileuton

II. LT receptor antagonists: Montelukast, Zafirlukast

III. Mast cell stabilizers: Sodium cromoglycate nedocromil.

(4) Other drugs that are under clinical trials:-

I. Anti IgE monoclonal antibodies: Omalizumab.

II. Calcium channel blockers: nifedipine, verapamil.

The medication can be administered orally or by inhalation. An inhalation method offers the advantage of delivery of high concentration of medication directly to the target organ. This results in a more rapid onset of pulmonary effects as well as fewer systemic effects compared with oral administration of the same dose. Various inhalation delivery systems are:-

1. Metered dose inhalers.
2. Dry powder inhaler.
3. Nebulizers.

COPD and Asthma medication can also be classified as:

I. Quick-Relief medication.

II. Long term control medication.

Quick-Relief Medication:- Short acting bronchodilators and systemic corticosteroids especially for Asthma comprise this group.

1. **Beta-adrenergic agonists**: Short acting $Beta_2$ selective adrenergic agonist includes salbutamol, terbutaline, bitolterol and pibuterol.
2. **Anticholinergics:** - These drugs reverse vagally mediated bronchospasm but not allergen or exercise induced bronchospasm. Tiotropium bromide, a quaternary derivative.

It may be useful adjunct to inhaled short acting B_2 agonist.

Dose - 18mcg once daily.

(3). **Phosphodiesterase inhibitors:**-Theophylline, a methyl xanthine is a commonly used drug for both COPD as well as bronchial asthma. It is not recommended for therapy of exacerbations.

Theophylline inhibits phosphodiesterase enzymes which catalyze the breakdown of cAMP and cGMP to 5'AMP and 5'GMP respectively. This will lead to accumulation of cAMP and cGMP causing relaxation of bronchial smooth muscles. Theophylline is a competitive antagonist at adenosine receptors. Adenosine causes bronchoconstriction and potentiates immunologically induced mediator release from lung mast cells. Inhibition of action of adenosine explains the mechanism of action of theophylline.

Dose- 12-16mg/kg/day.

(4). **Systemic Corticosteroids:** - These are less effective in case of COPD but these are effective in primary treatment for patients with moderate to severe exacerbations of asthma and for patients who fail to respond promptly and completely to inhaled to B_2 agonist therapy. Prednisolone is given at a dose of 40-60 mg/day as single dose or in two divided doses for 3-10 days. Severe exacerbations requiring hospitalization typically require 1mg/kg of prednisolone every 6-12 hrs for 48 hrs or until the FEV_1 returns to 50% of predicted.

Long term Control Medication:-

1. **Beta-adrenergic agonists:** - Long acting B_2 agonists like salmeterol are indicated for long term prevention of COPD symptoms and nocturnal symptoms and for prevention of allergen or exercise induced bronchospasm. They are used as adjuvant in inhaled corticosteroids.
   Dose- 50mcg /twice daily.
2. **Mast cell-stabilizing agents:** - These are mainly used in case of asthma. Cromolyn sodium and Nedocromil prevent symptoms and improve airway function in patients with COPD and exercise induced asthma.

They act by inhibiting degranulation of mast cells, there by preventing release of chemical mediators of anaphylaxis.

(3**). Leukotriene Modifier:** - Leukotrienes are biochemical mediators that contribute to airway obstruction. Montelukast and zafirlukast are crysteinyl leukotrienes receptor antagonists. Zileuton is 5-lipooxygenase inhibitor that decreases leukotrienes production.

These drugs can be considered as alternatives to low dose inhaled corticosteroids in the long term control of both the COPD as well as asthma.

Dose- tablet- Montelukast -10 mg daily in the evening.

(4). **Protease inhibitors**: - Neutrophil elastase inhibitors.

Alpha-1 antitrypsin- purified, by human recombinant gene transfer.

These are mainly used in advance treatment of COPD.

(5). **Corticosteroids**: - These are the most potent and consistently effective anti-inflammatory agents currently available. They reduce both acute and chronic inflammation, resulting in improvement in airflow decreased airflow hyper-responsiveness, fewer asthma symptoms exacerbations and less airway remodeling. Inhaled corticosteroids are preferred for the long term control and are first line drugs for the patients of asthma eg Budesonide, Fluticasone.

(6). **Antibiotics:** - Acute exacerbations of COPD are commonly assumed to be bacterial infection, since they may be associated with increased volume and purulent of the sputum. A meta-analysis of controlled trial of antibiotic in COPD showed a statistically significant but small benefit of antibiotics in terms of clinical outcome and lung function [31].

(7). **Oxygen:** - Long term oxygen therapy was justified by two large trials that showed reduced mortality and improvement in quality of life in patients with severe COPD and chronic hypoxemia. (Partial pressure of arterial oxygen < 55 mmHg)[(32)]. It is also effective treatment for asthma patients.

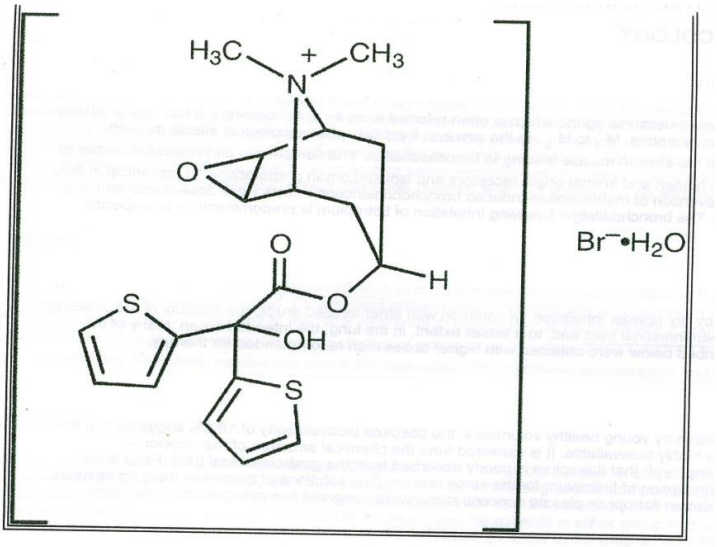
V. DRUG REVIEW

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.

VI. 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 M_3 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$^{(2,4)}$) Nonane bromide monohydrate.



Chemical structure of Tiotropium bromide

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 **C_{19} H_{22} NO_4 S_2 Br H_2O.**

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.

VII. HISTORICAL ASPECTS

The medicinal properties of naturally occurring anticholinergic agents such as atropine, found in many plants in the tropics and temperate climates, have been recognized for centuries. There are reports from India dating from the 17th century that describe the use of **Datura stramonium** leaves for the treatment of asthma from the 17th century. This plant arrived in Europe by the 19th century via British colonialists and was used to treat a wide assortment of breathing disorders, the anticholinergic agents, such as atropine and scopolamine, are readily absorbed from the respiratory and GI tracts and have significant side effects newer synthesized agents, such as ipratropium bromide, oxitropium bromide and tiotropium bromide have similar but modified chemical structures compared with naturally occurring anticholinergics. The drugs have significantly reduced systemic absorption and consequently, reduced side effects. Thus they are used broadly in the treatment of airway diseases, particularly COPD, as we understand the importance of the parasympathetic pathway's role in controlling airway tone. The most recent advance has been the introduction of the long-acting antimuscarinic, Tiotropium, developed by Boehringer Ingelheim, which included bronchodilatation lasting for several days. (Hansel & Barners, 2002).

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 FEV_1 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.

(1). 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 (quarternary 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.

(2). 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.

(3). Biotransformation: - 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 P_{450}-dependent oxidation and subsequent glutathione conjugation to a variety of phase-II metabolites. This enzyme pathway can be inhibited by CYP_{450} $2D_6$ and $3A_4$ inhibitors such as quinidine and ketoconazole.

Thus CYP_{450} 2D6 and $3A_4$ are involved in the metabolic pathway that is responsible for the elimination of a small part of administered dose.

(4). 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 M_1 to M_5. In the airways, it exhibits pharmacological effects through inhibition of M_3 receptors at the smooth muscle leading to bromchodilation.

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 innervation(Fig-3)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 (M_1) receptors. These neurons in turn release acetylcholine that stimulates muscarinic-3 (M_3) 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 both asthmatic and COPD patients experience when exposed to various environmental triggers. Muscarinic-2 (M_2) 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 M_3 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 and COPD 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 COPD and asthma. Furthermore, as outlined above, anticholinergic blockade of the M_2 receptors may actually promote further bronchoconstriction because of their feedback inhibition role. Unfortunately, most anticholinergic agents have no selectivity when it comes to stimulating M_1, M_2, or M_3 receptors. Tiotropium, a congener of ipratropium bromide, has been reported to bind avidly to M_1 and M_3 receptors while dissociating rapidly from M_2 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 atleast 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, methylaxanthines, 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.

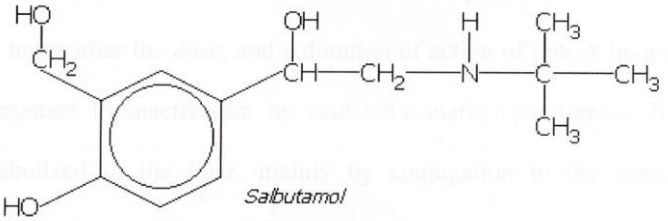
Warnings and precautions:- Tiotropium bromide should not be used for the initial treatment of acute episodes of bronchoconstriction i.e. rescue therapy. As with other anticholinergic drugs, Tiotropium bromide should be used with caution in patients with narrow-angle glaucoma, prostatic hyperplasia, bladder- 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 anticholingergic 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 $\mathbf{C_{13}\ H_{21}\ NO_3}$. It is a white crystalline powder sparingly soluble is water and freely soluble in ethanol. (Fig 5) chemical structure:-



(Fig-5)

Mechanism of Action:- Stimulation of $beta_2$ adrenoceptors in bronchial smooth muscle causes relaxation. These receptors are G protein coupled receptors. They bind to Gs protein and stimulate adenylyl cyclase there by causing accumulation of cAMP. cAMP causes activation of protein kinase-A. Protein kinase-A phosphorylates myosin Light chain kinase there by inactivating it. This lowers intra-cellular calcium concentration resulting in relaxation of smooth muscle.

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-4-0-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.

VIII. MATERIALS AND METHODS

The present clinical study was conducted in patients with stable as well as exacerbated COPD 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-IIIA, 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 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, FEV_1 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.

Exclusion Criteria for COPD

Patients with the following criteria were excluded from the study:-

1. Patients in the age group of less than 12 and more than 80 years of either sex.
2. Pregnant or lactating woman.
3. Subjects quit smoking less than 3 months prior to the screening visit.
4. Patients have clinically significant lung disease other than COPD and Bronchial Asthma

eg.Bronchectasis, acidosis, pulmonary fibrosis, tuberculosis etc.

5. Patients use oxygen > 2 liters per min for > 2 hrs / day.
6. Subjects have had cancer diagnosed or treated within the 5 years.
7. Patients require chronic or prophylactic treatment with antibiotics.
8. Subjects with significant renal, hepatic, cardiovascular (including corpulmonale), metabolic neurologic, hematologic, gastrointestinal, cerebrovascular or other significant medical illness or disorder which, in the judgment of the investigator, may interfere with the study or require treatment which may effect the evaluation of efficacy and safety of the drug study.
9. Patients with chronic narrow angle glaucoma.
10. Patients with symptomatic prostatic hyperplasia or bladder-neck obstruction.
11. Subjects have clinically significant abnormalities on chest x-ray.(Other than evidence of COPD / Br. Asthma) at the screening visit or within the previous year.
12. Patients with H/O Allergic rhinitis, myocardial infarction, increased total blood eosinophile count in COPD group patients.

Examination:-

Particulars of the patient like Name, age, address, occupation, and out patient number were_taken

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History:-

Detailed history was taken with special attention to the following points:-

- Cough; Expectoration; Haemoptysis; Breathlessness, wheezing; Nocturnal Awakening; Chest pain.
- Personal history – History of smoking, drinking.
- Allergy History – Food, house dust, traffic dust, perfumes, soaps, powders, hair dye and other.

Past History:-

I. History as similar complains in the past.
II. History of chronic bronchitis, pulmonary T.B., tropical pulmonary eosinophilia.
III. Diabetis mellitus, Hypertension, Chronic renal failure.
IV. Malignancy.

- Family history: - History of bronchial Asthma /COPD among 1st degree Relatives.
- Treatment history :-

(a). History of bronchodilator therapy , H / O Hospitalization.
(b). Corticosteroid therapy.

After the history was taken, a detailed clinical examination was done.

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 treated with 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:-

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

Score for frequency of Use of Rescue Medication [34]

O - < 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.

IX. 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 FEV_1 i.e. 0.22L, in FVC 0.31L and FEV_1/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, FEV_1 is improved by 0.21L, FVC by 0.31L and FEV_1/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 Bronchialasthmapatients.

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 TiotropiuminBronchialasthma.

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. Patient's compliance was good in all the 3 groups of patients.

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