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ROLE OF TIOROPIUM BROMIDE IN COPD

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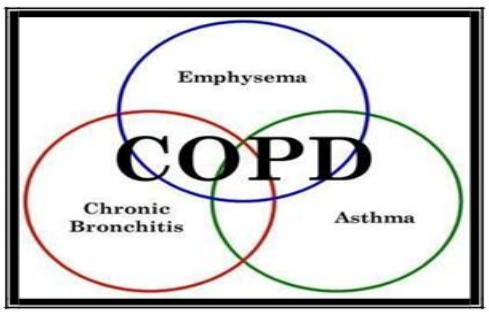
ABSTRACT

Inhaled bronchodilators are the mainstay of pharmacological treatment for stable chronic obstructive pulmonary disease (COPD), including β2-agonists and muscarinic antagonists. Tiotropium bromide, a long-acting antimuscarinic bronchodilator (LAMA), is a treatment choice for moderate-to-severe COPD; its efficacy and safety have been demonstrated in recent trials. Studies also point to a beneficial role of tiotropium in the treatment of difficult- to-control asthma and a potential function in the asthma-COPD overlap syndrome (ACOS). Combination of different bronchodilator molecules and addition of inhaled corticosteroids are viable therapeutic alternatives. It is important to recognize that while bronchodilators improve symptoms, a multimodality treatment approach including respiratory and rehabilitative therapy, nutrition services, psychosocial counseling, and surgical care, is often necessary for the best possible care of patients with COPD.

KEYWORDS: Tiotropium bromide, Stiolto Respimat, COPD, anticholinergic, beta2 agonist.

INTRODUCTION



Chronic obstructive pulmonary disease (COPD), a relatively common respiratory disorder in the U.S., is the third leading cause of death in this country. It has been estimated that 15 million Americans have COPD. Since the disorder is so common, effective treatment regimens are a prominent research topic in pharmacology. Still, the development of pharmacological treatments for COPD has been a struggle. Only recently has sufficient progress been made in understanding the molecular and cell biology of COPD to allow the identify caution of new therapeutic targets. Currently, no drugs can reverse the progression of COPD. Hence, the development of new monotherapies or combination therapies is pivotal in providing relief to these patients.

Several drug classes are used to treat COPD, including anticholinergic agents, short- and long-acting beta2 agonists (LABAs), inhaled corticosteroids, and phosphodiesterase 4 (PDE4) inhibitors.

Since COPD is most commonly caused by smoking and by exposure to secondhand smoke, the predominant non pharmacological treatment is smoking cessation. Patients are also advised to avoid other triggers that may worsen respiration, such as air pollution, pet dander, and noxious chemicals.

Because COPD is a progressive, debilitating disorder, patients commonly rely on combination therapies for relief. Of the available combination products, anticholinergic agents plus LABAs are often used for maintenance treatment.

Anticholinergics work primarily by inhibiting the action of acetylcholine and by reducing cyclic-adenosine monophosphate (cAMP) in bronchial smooth muscles, thereby triggering bronchodilation. LABAs bind to beta-adrenergic receptors, resulting in the relaxation of bronchial smooth muscles.3 When drugs from these two classes are used in combination, they have a synergistic effect on bronchodilation and improve airflow throughout the respiratory system. Tiotropium bromide inhalation spray (Stiolto Respimat, Boehringer Ingelheim), approved in May 2015 by the Food and Drug Administration, is a new fixed-dose anticholinergic/LABA combination medication for patients with COPD.

Molecular Biology

Muscarinic receptors have been classified into five subtypes, initially based on drug selectivity, and subsequently confirmed by molecular cloning. M1, M2 and M3 receptors are

found in human airways. M1 receptors are found in alveolar walls and in the parasympathetic airway ganglia, their blockade reduces the bronchoconstriction response. M2 receptors are located on postganglionic cholinergic nerve endings, and these auto-receptors limit the magnitude of vagally induced bronchoconstriction. M3 receptors are located on airway smooth muscle and submucosal glands, where they mediate bronchoconstriction and mucus secretion. Muscarinic acetylcholine receptors are G protein-coupled receptors (GPCRs). M1 and M3 are coupled with Gq proteins, while M2 are coupled with Gi/o proteins. Tiotropium bromide is an inhaled long-acting muscarinic antagonist (LAMA). It has a high affinity and dissociates very slowly from M1 and M3 receptors, and more rapidly from M2 receptors. It produces long-term blockade of cholinergic neural bronchoconstriction in human airways, providing 24-h bronchodilatation.

Tiotropium Bromide

The effect of tiotropium dry powder for inhalation on the QT interval was evaluated in a randomized, placebo- and positive-controlled crossover study in 53 healthy volunteers. The subjects received tiotropium inhalation powder 18 mcg (the recommended dose), 54 mcg, or placebo for 12 days. ECG assessments were performed at baseline and throughout the dosing interval following the first and last dose of study medication. Compared with placebo, the maximum mean changes from baseline in the QTc interval were 3.2 msec and 0.8 msec for tiotropium inhalation powder 18 mcg and 54 mcg, respectively. None of the subjects had QTc intervals of greater than 500 msec or QTc changes from baseline of 60 msec or more.

Tiotropium dry powder was also evaluated in a multicenter, randomized, double-blind trial involving 198 patients with COPD. In this study, the number of subjects with changes from the baselinecorrected QT interval of 30 to 60 msec was higher in the tiotropium group than in the placebo group. This betweengroup difference was established using both QTcB (20 patients [20%] versus 12 patients [12%]) and QTcF (16 patients [16%] versus one patient [1%]). None of the patients in either group had either a QTcB or QTcF of greater than 500 msec. Other clinical studies did not detect an effect of tiotropium on QTc intervals.

Mechanism of Action

As an anticholinergic agent, tiotropium bromide antagonizes the effect of acetylcholine in the bronchioles to prevent bronchoconstriction and to trigger bronchodilation. In preclinical in vitro investigations as well as in vivo studies, the prevention of methacholine-induced bronchoconstriction was dose-dependent and lasted longer than 24 hours. The

bronchodilation following inhalation of tiotropium is predominantly a site-specific effect. After topical administration by inhalation, the tiotropium binds to beta2-adrenergic receptors in the bronchioles and triggers smooth-muscle relaxation, resulting in bronchodilation.

Effect on Cardiac Electrophysiology

In two 52-week, randomized, doubleblind trials of fixed-dose tiotropium electrocardiograph (ECG) assessments were performed after dosing on days 1, 85, 169, and 365 in a total of 5,162 patients with COPD. In a pooled analysis, the numbers of subjects with changes from baseline-corrected QT interval of greater than 30 msec, using both the Bazett (QTcB) and Fredericia (QTcF) corrections of QT for heart rate, were not different for the tiotropium group compared with tiotropium 5 mcg alone across the assessments conducted.

Pharmacokinetics

When tiotropium was administered by inhalation, the pharmacokinetic parameters for the two components were similar to those observed when each substance was administered separately. Some of the pharmacokinetic data described below were obtained with dosages that were higher than the recommended dosage of two inhalations per day.

Absorption and Distribution

After inhalation of a tiotropium solution by young, healthy volunteers, urinary excretion data indicated that approximately 33% of the inhaled dose reaches the systemic circulation. Oral solutions of tiotropium have an absolute bioavailability of 2% to 3%. Food is not expected to influence the absorption of tiotropium. Maximum tiotropium plasma concentrations are observed five to seven minutes after inhalation.

Tiotropium is 72% plasma proteinbound and has a volume of distribution of 32 L/kg. Lung concentrations are unknown, but the mode of administration suggests substantially higher concentrations in the lung. In rats, tiotropium did not cross the blood–brain barrier.

Metabolism and Elimination

In vitro experiments with human liver microsomes and human hepatocytes suggest that a fraction of the administered dose of tiotropium is metabolized by cytochrome P450 (CYP450)-dependent oxidation and subsequent glutathione conjugation to a variety of phase 2 metabolites. Tiotropium, an ester, is nonenzymatically cleaved to the alcohol N-methylscopine and to dithienylglycolic acid, neither of which binds to muscarinic receptors.

This enzymatic pathway can be inhibited by CYP2D6 and 3A4 inhibitors, such as quinidine, ketoconazole, and gestodene.

Excretion

The terminal half-life of tiotropium in COPD patients after once-daily inhalation of 5 mcg is approximately 25 hours. Total clearance was 880 mL/min after an IV dose in young, healthy volunteers. IV tiotropium bromide is mainly excreted unchanged in urine (74%). After inhalation of the solution, urinary excretion is 19% of the dose; the remainder is mainly nonabsorbed drug in the gut, which is eliminated via the feces. The renal clearance of tiotropium exceeds the creatinine clearance, indicating secretion into the urine. After chronic once-daily inhalation by COPD patients, pharmacokinetic steady state was reached by day 7, with no accumulation thereafter.

Tiotropium Mechanism of Action in COPD

COPD is an inflammatory disease, and during exacerbations a further intensified inflammatory response occurs. As mentioned, tiotropium has been shown to prolong the time to first exacerbation, compared to placebo, in addition to reducing the frequency of exacerbations and associated hospitalization. It is known that acetylcholine increases neutrophil chemotactic activity in COPD, and that this effect is attenuated in vitro by tiotropium, suggesting a possible anti-inflammatory mechanism, though it remains controversial.

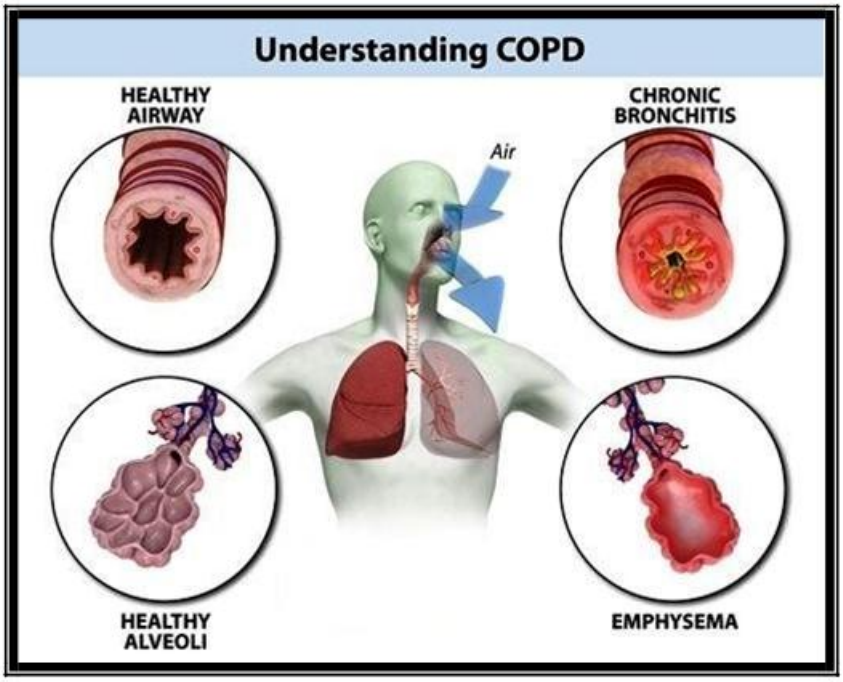
A British study including 142 patients, randomized either to receive tiotropium or placebo for 1 year, failed to demon strate a reduction in airway or systemic inflammatory markers. Of the three sputum inflammatory markers: interleukin-6 (IL6), interleukin-8 (IL-8) and myeloperoxidase, none was found to be reduced after tiotropium therapy; in fact, IL-8 levels were found to be increased. This results could be attributed to the fact that tiotropium causes reduced production of mucus in the airway, increasing the concentration of cytokines. This also suggests that the measurement of cytokines in sputum is not an optimal method to assess airway inflammation.

Tiotropium reduces the volume of secretions, but does not alter the viscoelastic properties of mucus. In vitro studies show that acetylcholine induces the release of inflammatory mediators, such as the granulocyte-macrophage colony stimulating factor (GM-CSF), leukotriene B4 (LTB4) and prostaglandin E2 of epithelial cells. This release is mediated via

muscarinic receptors that could be inhibited by tiotropium. In the British study mentioned above, levels of LTB4 or GM-CSF were not measured, and they seem to be more relevant to evaluate cholinergic effects.

There is also evidence that tiotropium may prevent contractility and proliferation of airway smooth muscle cells and fibroblast proliferation. These findings support the hypothesis that the cholinergic system has a role in the pro-fibrotic processes of airway remodeling. Peribronchiolar fibrosis may be a key event in the progressive FEV1 decline in COPD. Any inhibitory effect of tiotropium in the development of fibrosis may be detectable only after several years of treatment, as a slow decline in lung function. Long-term studies are not available, but clinical evidence points towards muscarinic antagonists having an anti-inflammatory effect and/or an effect on airway remodeling in COPD.

Treatment According to Disease Stage



Spirometry should be used to help identify and stage patients with COPD as their treatment is often predicated upon disease stage (Figure 5) (Lipson 2004). However, following stable patients with multiple repeat spirometric tests may not be useful (Wilt et al 2005). “At risk” patients must refrain from cigarette smoking, and should obtain annual infl uenza vaccination and should be vaccinated with the pneumococcal vaccine every 5 years. Bronchodilator therapy on an “as needed” basis with short-acting bronchodilators may be used for managing mild COPD patients (Vathenen et al 1988).

A combination of short- and long-acting bronchodilators is often used to treat moderate emphysema. Inhaled anticholinergic medications and combinations of short- and long-acting β2-agonists are standard treatments. Inhaled corticosteroids may be useful for patients with more severe disease, or those patients with a partially reversible, bronchospastic component to airfl ow obstruction. These medications may also be useful in patients who have repeated exacerbations (Burge et al 2000; The Lung Health Study Research Group 2000; Sin and Tu 2001; Hattotuwa et al 2002). Medications combining an inhaled steroid and a long-acting β-agonist, such as fl uticasone and salmeterol, may also be useful in this patient population

(Mahler et al 2002). Pulmonary rehabilitation is an important addition to pharmacologic therapy in patients with COPD because severe dyspnea leads to a sedentary lifestyle, subsequent deconditioning, and muscle weakness (ACCP/AACVPR Pulmonary Rehabilitation Guidelines Panel 1997).

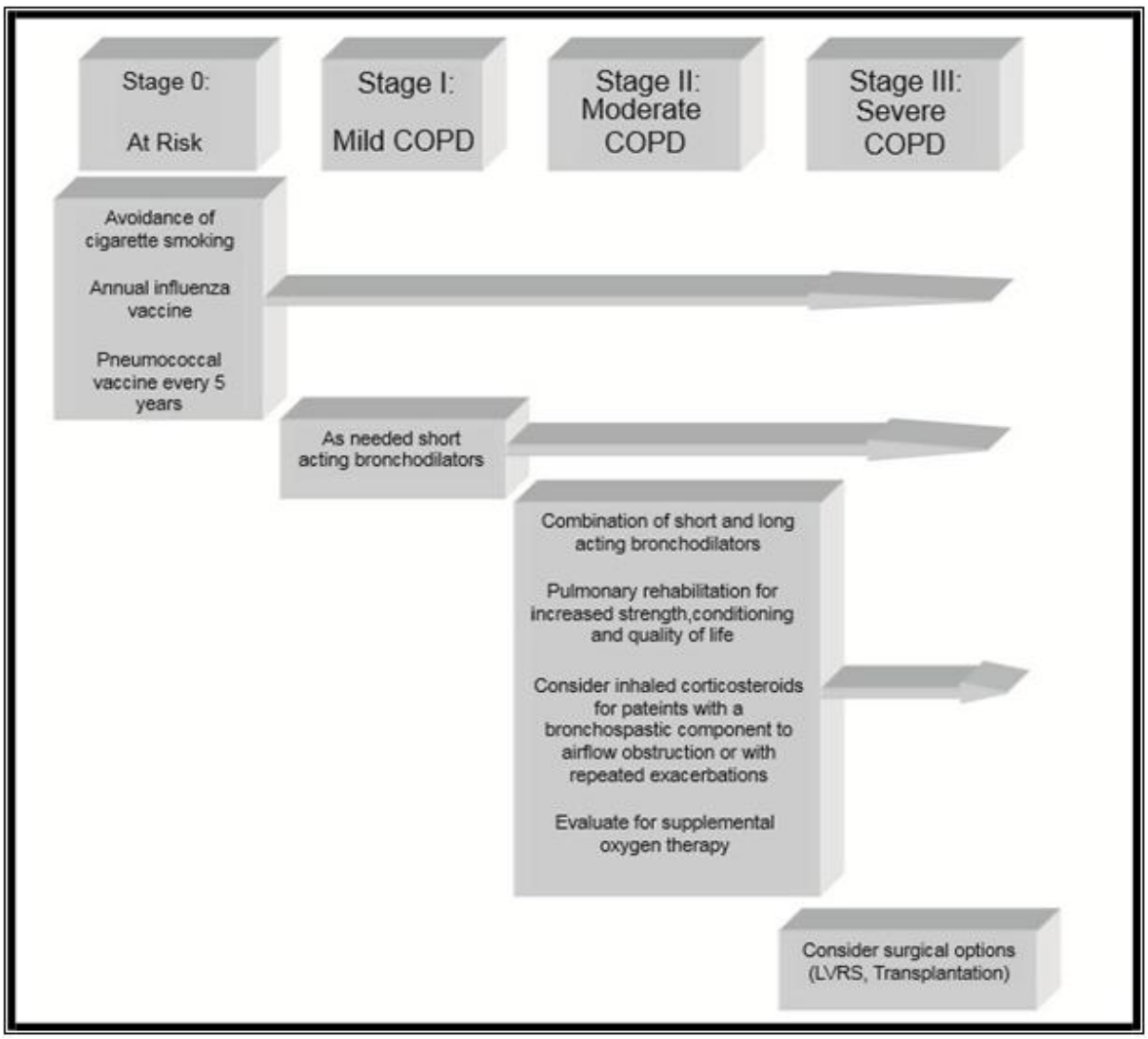


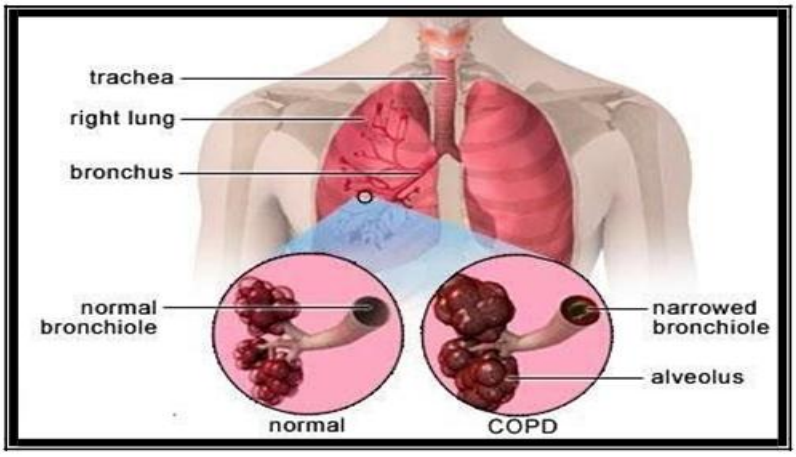
Figure 5: Treatment of COPD by stage.

Pulmonary rehabilitation increases strength, quality of life, sense of well-being, and exercise tolerance. It is also useful in breaking the vicious cycle of progressive debilitation in patients with advanced lung disease (Fishman 1994; Celli 1997; ATS 1999).

All patients with moderate COPD should be evaluated for the need for supplemental oxygen. Patients who exhibit oxyhemoglobin desaturation at rest, or with exertion, should be prescribed supplemental oxygen to maintain oxyhemoglobin saturations greater than 90%.

Long-term oxygen therapy, in COPD patients who require it, has been shown to improve survival, exercise tolerance, and quality of life (Nocturnal Oxygen Therapy Trial Group 1980; Medical Research Council Working Party 1981; Tarp and Celli 1995). A patient requires supplemental oxygen if they demonstrate an oxyhemoglobin saturation < 88% or a PaO2 < 55 mmHg. Additionally, an oxyhemoglobin saturation < 89% or a PaO2 < 60 mmHg also qualifi es a patient for supplemental oxygen if there is evidence of cor pulmonale, a hematocrit > 56%, dependent edema, or other signs suggestive of heart failure.

The treatment of severe COPD is equivalent to that of moderate disease, except patients in this stage should also be evaluated for potential surgical treatments such as lung volume reduction surgery or lung transplantation (Cooper et al 1996; Sciurba et al 1996; Arcasoy and Kotloff 1999; Criner et al 1999; Geddes et al 2000; Flaherty et al 2001; Kotloff et al 2001; National Emphysema Treatment Trial Research Group 2001, 2003).



Tiotropium in COPD Smokers

COPD is a major cause of morbidity and mortality, and many people suffer from this disease for years and die prematurely from it or its complications. Cigarette smoking is the most important single risk factor for COPD in the developed world. Treatment of COPD is now

aimed at immediately relieving and reducing the impact of symptoms, as well as reducing the risk of future adverse health events, such as exacerbations. In this section, the role of tiotropium in COPD smokers will be discussed.

The UPLIFT trial is a 4-year randomized placebo-controlled study, and it was performed in moderate to very severe COPD patients treated once a day with 18 µg inhaled tiotropium (dry powder, HandiHaler®). The study showed significant improvement in lung function and health-related quality of life and a reduction of exacerbations and hospitalization. But tiotropium did not significantly reduce the rate of decline in FEV1 or mortality compared to placebo ($P \leq 0.09$).

The results could be explained by several reasons. One possible explanation is that tiotropium does not influence the decline in lung function over time. In this context, data suggest that the symptomatic and functional improvement arise from mechanisms other than those identified to prolong life. It could also be that factors not yet been identified have an influence on mortality, and that they do not respond to tiotropium therapy.

It is also important to consider that, in the design of the UPLIFT study, the high rate of simultaneous prescription of other respiratory drugs may have affected the decline in lung function. This has been described as a ceiling effect, in which further improvements are not observed in the absence of an intervention that repairs or regenerates lung tissue. The group of patients who received tiotropium but did not receive inhaled glucocorticoids (IGCs) or long-acting β2 agonists (LABAs), did show a statistically significant improvement in the decline rate in FEV1 ($P \leq 0.046$), supporting this justification. Another explanation is the higher rate of discontinuation in the placebo group. Patients who discontinued treatment had, on average, significantly more severe airflow obstruction at the beginning of the study. Consequently, those in the placebo group that completed the study may represent "healthy survivors".

In the UPLIFT study, tiotropium was associated with a decrease in respiratory morbidity (dyspnea and risk of respiratory failure) and cardiac morbidity (heart failure and acute myocardial infarction). Additionally, tiotropium was not associated with an increased incidence of pneumonia or stroke, opposite to what was previously reported in a meta-analysis. These findings were supported by the Food and Drug Administration (FDA). Nevertheless, there were still some concerns about its cardiovascular safety, and some

researchers raised the need for controlled and randomized studies with greater statistical power.

The TIOSPIR trial is a randomized double-blind study involving 17,135 COPD patients. The study compared patients treated with Respimat® in inhaler (daily doses of 2.5 and 5.0 µg) to a control group using Handi Haler® (18 µg daily). In this trial, Respimat® was not inferior to Handi Haler® regarding risk of death, nor was it better than Handi Haler® regarding the time of first exacerbation. In fact, comparative risk ratios were very close to 1, with 95% confidence intervals (CIs). In other words, the three doses with two different devices are comparable in terms of safety and efficacy.

In addition to the statistical power of the sample, one of the most relevant aspects of the TIOSPIR study is that it enrolled a substantial number of patients with cardiac conditions (1,825 with arrhythmia and 3,152 with ischemic heart disease, coronary artery disease or heart failure). The tiotropium Respimat® did not increase the risk of death or adverse events in these patients. The tiotropium Handi Haler® was associated with a reduced mortality, eve n in patients with coexisting heart disease.

Former meta-analysis and observational studies identified up to a 52% increased risk of cardiovascular mortality in COPD patients treated with Respimat®, particularly in patients who had persistent arrhythmia, cardiomegaly or chronic renal failure. Some authors even recommended that Respimat® should not be prescribed to patients with COPD, but these authors subsequently endorsed TIOSPIR results. Respimat® generates a fine aerosol cloud (Soft Mist Inhaler) that moves very slowly (4 - 10 times slower than a pressurized inhaler), with a high proportion of the emitted dose deposited in the lung. It was then presumed that a high systemic exposure could occur, which would explain the apparent increase in mortality; nonetheless, pharmacokinetic studies show similar systemic exposure to the drug, regardless of the delivery system.

The results of TIOSPIR show that caution should be exercised in interpreting the safety outcomes of meta-analysis and observational studies; these are merely post hoc studies without a prior hypothesis. Randomized clinical trials balance the confounding factors of observational studies, and lead to more realistic outcomes.

Tiotropium in COPD Non –Smokers

Of the patients with COPD, 25-45% have never smoked. In these patients, the most important identifiable risk factors include exposure to biomass fuel, occupational exposure to dust and fumes, history of pulmonary tuberculosis or chronic asthma, outdoor pollution and poor socioeconomic status. Approximately 3 billion people (half the world's population) are exposed to smoke from biomass fuels, compared to 1.01 billion people who smoke tobacco; consequently, exposure to biomass smoke might even be the biggest risk factor for COPD globally, as it is in developing countries.

Biomass is a solid fuel used for heating and for cooking in open fire stoves, which is composed of plants (wood, coal, crop, twigs, and dried grass) and animal residues (dung). Developing countries burn about 2 billion kilograms of biomass per day. The smoke emitted contains a number of pollutants: particulate matter (PM2.5, PM10), carbon monoxide, nitrogen dioxide (NO2), sulfur dioxide, formaldehyde and polycyclic organic matter. These pollutants are similar to those present in tobacco smoke, and they start the inflammatory process in small airways and lung parenchyma. In developing countries, about 50% of COPD deaths are related to biomass smoke, 75% of which are in women. The World Health Organization declared the environmental pollution from biomass as one of the top 10 health risks, as it is responsible for 1.5 million deaths annually.

In Turkey, studies among non-smoking women exposed to biomass smoke have shown a direct relationship between the decline in FEV1 and exposure in hours/year to wood (province of Anatolia and Black Sea) and dung (East Anatolia). Over 80% of households in China, India, and Sub-Saharan Africa use biomass fuel for cooking, and in rural areas of Latin America the proportion varies between 30% and 75%. In developed nations like Canada, Australia and in western states of the US, the rising cost of energy has led to an increase in the number of households using wood and other biomass for heating.

Few studies have compared the phenotype of COPD in non-smokers to smokers. In a Mexican work, women who had COPD and had been exposed to smoke from biomass fuel had similar clinical characteristics, quality of life, and mortality to those with smoking-related COPD. Shavelle and colleagues found that in the US, never-smokers had a reduction in life expectancy when compared to smokers. Moran Mendoza and colleagues reported that women with COPD due to biomass smoke have more pulmonary fibrosis, increased pigment

deposition and greater pulmonary intimal thickening than women with COPD due to tobacco smoking.

Several questions need to be answered about this COPD phenotype, including the real burden in different countries, the clinical, radiological and functional characteristics, the cellular and immunological profiles, the prognosis and particularly, if the treatment should be the same. In this sense, there are no studies of the use of anticholinergics in these patients. Given that tobacco smoking has been considered the leading cause of COPD in developed countries, research protocols not related to tobacco are lacking.

Safety Profile

Adverse Events in COPD

The primary safety database for tiotropium consists of pooled data from the two 52-week confirmatory studies described previously. These studies included a total of 1,029 patients who were treated with tiotropium/olodaterol once daily. Tiotropium 5 mcg and olodaterol 5 mcg were included as active control arms in both studies; no placebo treatments were used.

In these two clinical studies, 74.0% of the patients treated with tiotropium reported an adverse event, compared with 76.6% and 73.3% of the tiotropium groups, respectively. The most common adverse events were nasopharyngitis (12.4% for tiotropium, 11.7% for tiotropium), cough (3.9%, 4.4%, and 3.0%), and back pain (3.6%, 1.8%, and 3.4%). In both studies, the most common serious adverse events were COPD exacerbation and pneumonia. The proportions of patients who discontinued treatment because of an adverse event were 7.4% for the tiotropium/olodaterol group, 9.9% for the olodaterol group, and 9.0% for the tiotropium group. The adverse event most commonly leading to discontinuation was worsening COPD.

Drug-Drug Interactions

Several drugs, including adrenergic agents, sympathomimetics, and non– potassium-sparing diuretics, should be used with caution with fixed-dose tiotropium/olodaterol because of the potential for adverse drug–drug interactions. These medications are listed in Table 1.

Contraindications

All LABAs, including olodaterol, increase the risk of asthma-related death and are contraindicated in patients with asthma without the use of a long-term asthma-control

medication. Fixed-dose tiotropium is not indicated for the treatment of asthma. Further, fixeddose tiotropium is contraindicated in patients with a hypersensitivity to tiotropium, ipratropium, or any component of the product.

Immediate hypersensitivity reactions, including angioedema, itching, and rash, have been reported in both clinical trials and post-marketing experience with tiotropium monotherapy. Hypersensitivity reactions were also reported in clinical studies of fixed-dose tiotropium.

Table 1 Drugs With a Potential to Interact With Fixed-Dose Tiotropium/Olodaterol[4]

Agent	Potential Interactions
Adrenergic drugs	Coadministration with tiotropium/olodaterol may potentiate sympathetic effects of olodaterol.
Anticholinergic drugs	Coadministration with tiotropium/olodaterol may increase anticholinergic adverse effects.
Beta-adrenergic receptor antagonists	Beta blockers and olodaterol (a beta-adrenergic receptor agonist) may interfere with each other's effects when administered concurrently. Beta blockers inhibit therapeutic effects of beta agonists and may produce severe bronchospasm in COPD patients.
Diuretics	Coadministration with tiotropium/olodaterol may potentiate hypokalemic effects of olodaterol.
Non–potassium-sparing diuretics	ECG changes and/or hypokalemia may result from coadministration of non–potassium-sparing diuretics and beta agonists, such as olodaterol.
QTc-prolonging agents	Action of adrenergic agonists, such as olodaterol, may be potentiated by QTc-prolonging agents, such as monoamine oxidase inhibitors and tricyclic antidepressants. Drugs that prolong QTc interval may increase risk of ventricular arrhythmias.
Steroids	Coadministration with tiotropium/olodaterol may potentiate hypokalemic effects of olodaterol.
Sympathomimetic drugs	Coadministration with tiotropium/olodaterol may potentiate hypokalemic effects of olodaterol.
Xanthine derivatives	Coadministration with tiotropium/olodaterol may potentiate hypokalemic effects of olodaterol.

COPD = chronic obstructive pulmonary disease; ECG = electrocardiogram

Key Warnings and Precautions

Asthma-Related Death

Data from a large placebo-controlled study in asthma patients showed that long-acting beta2-adrenergic agonists may increase the risk of asthma-related death. No studies have been conducted to determine whether the rate of asthma-related death is increased in patients treated with tiotropium. As noted above, tiotropium is contraindicated in asthma patients.

Deterioration of COPD

Treatment with tiotropium should not be initiated in patients with acutely deteriorating COPD because the drug has not been studied in this population. Moreover, tiotropium/olodaterol should not be used to relieve acute symptoms of COPD, i.e., as rescue therapy for the

treatment of acute episodes of bronchospasm. When prescribing tiotropium, health care providers should also prescribe an inhaled, short-acting beta2 agonist in case rescue therapy is needed, and they should instruct patients on how and when to use it.

Paradoxical Bronchospasm

As with other inhaled drugs containing beta2-adrenergic agents, tiotropium may cause paradoxical bronchospasm, which may be life-threatening. If paradoxical bronchospasm occurs, tiotropium should be stopped immediately and an alternative therapy instituted.

Cardiovascular Effects

Tiotropium, like other beta2 agonists, can produce a clinically significant cardiovascular effect in some patients, as measured by increases in pulse rate, systolic or diastolic blood pressure, and or other cardiovascular symptoms. If such effects occur, tiotropium may need to be discontinued. In addition, beta agonists have been reported to produce ECG changes, such as prolongation of the QTc interval, but the clinical significance of these findings is unknown. LABAs should be administered with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, hypertrophic obstructive cardiomyopathy, and hypertension.

Worsening of Narrow -Angle Glaucoma

Tiotropium should be used with caution in patients with narrow-angle glaucoma. Prescribers and patients should be alert for signs and symptoms of acute narrow-angle glaucoma. If any of these signs or symptoms should develop, the patient should consult a physician immediately.

Worsening of Urinary Retention

Tiotropium should be used with caution in patients with urinary retention. Prescribers and patients should be alert for signs and symptoms of prostatic hyperplasia or bladder-neck obstruction, such as difficulty passing urine or painful urination. If any of these signs or symptoms should develop, the patient should consult a physician immediately.

Renal Impairment

Because tiotropium is mainly excreted via the kidneys, patients with moderateto-severe renal impairment (i.e., those with a creatinine clearance of 60 mL/min or less) treated with tiotropium/olodaterol should be monitored closely for anticholinergic effects.

Hypokalemia and Hyperglycemia

Beta-adrenergic agonists may produce significant hypokalemia in some patients, which can result in adverse cardiovascular effects. This decrease in serum potassium is usually transient and does not require supplementation. The inhalation of high doses of beta2-adrenergic agonists may increase plasma glucose levels. Clinically relevant decreases in serum potassium or changes in blood glucose occurred infrequently during clinical trials involving the long-term administration of olodaterol, with rates similar to those of placebo-treated controls.

Indication and Usage

Tiotropium bromide is indicated for the long-term, once-daily maintenance therapy of airflow obstruction in patients with COPD. It is not indicated to treat asthma or acute deterioration o f COPD.

Dosage and Administration

The recommended dose of tiotropium is two inhalations once daily at the same time of the day. Tiotropium should not be used at more than two inhalations every 24 hours. Before the first use, the tiotropium cartridge is inserted into the Stiolto Respimat inhaler and the unit is primed. When using the unit for the first time, patients should actuate the inhaler toward the ground until an aerosol cloud is visible, and then repeat the process three more times. The unit is then considered primed and ready to use. If it is not used for more than three days, patients should actuate the inhaler once to prepare the inhaler for use. If it is not used for more than 21 days, patients should actuate the inhaler until an aerosol cloud is visible and then repeat the process three more times to prepare the inhaler for use.4 No dosage adjustment is required for geriatric, hepatically impaired, or renally impaired patients. However, patients with moderate-to-severe renal impairment treated with tiotropium should be monitored closely for anticholinergic effects.

Cost

The average wholesale price (AWP) of one tiotropium inhalation device is $379. Each device supplies 60 metered inhalations of 2.5/2.5 mcg per actuation, meaning it should last 30 days using the recommended regimen of two inhalations per day.

CONCLUSIONS

Tiotropium bromide is a safe and efficient bronchodilator in the treatment of moderate to very severe COPD. It is plausible that this drug will have the same benefits in the treatment of COPD in non-smokers than in smokers, but this still requires demonstration. These medications improve quality of life measures and reduce the risk of exacerbation (Barr et al 2005).

Clearly, the best treatment of COPD remains smoking cessation and abstinence from smoking. Evaluation and care of the patient with COPD must include respiratory and rehabilitative therapy, nutrition services, psychosocial counseling, and evaluation for the need for long-term oxygen therapy. Physicians, and persons charged with caring for patients with COPD, await the development of novel therapies that will further improve survival, and the quality of the lives of patients with lung disease.

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