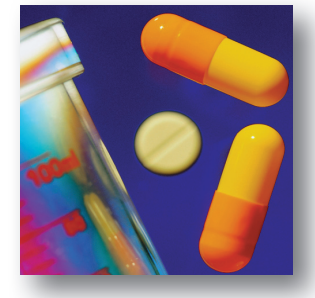

Tiotropium Bromide/Olodaterol (Stiolto Respimat)

Once-Daily Combination Therapy for the Maintenance of COPD

Juan F. Mosley II, PharmD, CPh, AAHIVP; Lillian L. Smith, PharmD, CPh, MBA; and Brittany N. Dutton, PharmD Candidate

Keywords: tiotropium bromide, olodaterol, Stiolto Respimat, COPD, anticholinergic, beta$_2$ 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.[1] It has been estimated that 15 million Americans have COPD.[1] 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 identification of new therapeutic targets.[2] Currently, no drugs can reverse the progression of COPD.[2] 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 beta$_2$ agonists (LABAs), inhaled corticosteroids, and phosphodiesterase 4 (PDE4) inhibitors.[3]

Since COPD is most commonly caused by smoking and by exposure to secondhand smoke, the predominant nonpharmacological 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.[3]

Because COPD is a progressive, debilitating disorder, patients commonly rely on combination therapies for relief.[2] 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

Dr. Mosley and Dr. Smith are Assistant Professors of Pharmacy Practice at the Florida Agricultural and Mechanical University, College of Pharmacy and Pharmaceutical Sciences, in Crestview, Florida. Brittany Dutton is a Doctor of Pharmacy candidate at that institution. Drug Forecast is a regular column coordinated by Alan Caspi, PhD, PharmD, MBA, President of Caspi & Associates in New York, New York.

Disclosure: The authors report no commercial or financial interests in regard to this article.

GLOSSARY

Actuation—in an inhaler, the process by which a single dose is released for patient use.

Acutely deteriorating COPD—a sustained worsening of the patient's condition, from stable state and beyond normal day-to-day variations, that is sudden in onset and may warrant additional treatment; also called an exacerbation.

Bazett corrections of QT (QTcB)—standard formula used to correct the observed QT interval in an electrocardiogram based on cardiac rate. The Bazett formula is: QT = Q-Tsec/√RR sec.

Bronchodilation—expansion of the air passages to the lungs (bronchioles and bronchi) to provide better air flow.

Cardiac electrophysiology—process that records electrical transmissions through the heart; used mainly to diagnose cardiac arrhythmias such as QT-interval prolongation.

Chronic bronchitis—inflammation of mucous membranes leading to excess mucus production and development of a chronic, productive cough; associated with vulnerability to lung infections.

Chronic obstructive pulmonary disease (COPD)—group of respiratory diseases characterized by the chronic obstruction of airflow to the lungs and not fully reversible; chronic bronchitis and emphysema are major forms of COPD.

Emphysema—abnormal enlargement of air sacs (alveoli) in the lungs that can progressively damage tissue; characterized by breathlessness.

FEV$_1$—forced expiratory volume in one second, the volume of air that can be forcefully expired in that time after a full, deep inhalation.

FEV$_1$/FVC ratio—percentage of the total FVC that is expelled from the lungs during the first second of a forced exhalation.

Fredericia corrections of QT (QTcF)—alternative formula used to correct the observed QT interval in an electrocardiogram based on cardiac rate. The Fredericia formula is: QT = QT/(RR^0.33).

FVC—forced vital capacity, the total volume of air that can be forcefully expelled after a full, deep inhalation.

Millisecond (msec)—one-thousandth of a second.

Priming (an inhaler)—spraying one or more puffs into the air prior to using the inhaler initially or after an extended period of disuse to ensure proper dose delivery.

Respimat Soft Mist inhaler—new-generation, propellant-free inhaler that allows a patient to inhale normally and still achieve increased lung penetration.

Spirometry—test of the lungs' air capacity in terms of the volumes of air inspired and expired. Spirometric criteria are used by the COPD GOLD guidelines to classify the severity of the illness: mild disease, FEV$_1$ ≥ 80%; moderate disease, FEV$_1$ ≥ 50% but < 80%; severe disease, FEV$_1$ ≥ 30% but < 50%; very severe disease, FEV$_1$ < 30%.

St. George's Respiratory Questionnaire (SGRQ)—50-item survey for patients with chronic respiratory illnesses to assess the impact of obstructive airway diseases on overall health, daily life, and perceived well-being. Scores range from 0 to 100; higher numbers equate to more limitations.

Thyrotoxicosis—overproduction of thyroid hormones in the body; hyperthyroidism is a type of thyrotoxicosis.

the respiratory system.[3] Tiotropium bromide/olodaterol 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.[4]

INDICATION AND USAGE

Tiotropium bromide/olodaterol 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 of COPD.[4]

MECHANISM OF ACTION

As an anticholinergic agent, tiotropium bromide antagonizes the effect of acetylcholine in the bronchioles to prevent bronchoconstriction and to trigger bronchodilation.[7] 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.[4] After topical administration by inhalation, the LABA olodaterol binds to beta$_2$-adrenergic receptors in the bronchioles and triggers smooth-muscle relaxation, resulting in bronchodilation.[4,8]

EFFECT ON CARDIAC ELECTROPHYSIOLOGY

In two 52-week, randomized, double-blind trials of fixed-dose tiotropium/olodaterol, 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/olodaterol group compared with olodaterol 5 mcg alone and tiotropium 5 mcg alone across the assessments conducted.[4]

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.[4]

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 baseline-corrected QT interval of 30 to 60 msec was higher in the tiotropium group than in the placebo group. This between-group 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.[4]

Olodaterol Hydrochloride

The effect of olodaterol on the QT/QTc interval was investigated in 24 healthy male and female volunteers in a double-blind, randomized, placebo- and active-controlled (moxifloxacin) study at single doses of 10, 20, 30, and 50 mcg. Dose-dependent QtcI (the individual subject-corrected QT interval) prolongation was observed. The maximum mean (one-sided 95% upper confidence bound) differences in QTcI from placebo after baseline corrections were 2.5 (5.6) msec, 6.1 (9.2) msec, 7.5 (10.7) msec, and 8.5 (11.6) msec after doses of 10, 20, 30, and 50 mcg, respectively.[4]

The effects of 5 mcg and 10 mcg of olodaterol on heart rate and rhythm were assessed using continuous 24-hour ECG recording (Holter monitoring) in 772 patients. No dose- or time-related trends or patterns were observed for the magnitudes of mean changes in heart rate or premature beats. Shifts from baseline to the end of treatment in premature beats did not indicate clinically meaningful differences among olodaterol 5 mcg, olodaterol 10 mcg, and placebo.[4]

PHARMACOKINETICS

When tiotropium/olodaterol was administered by inhalation, the pharmacokinetic parameters for the two components were similar to those observed when each substance was administered separately.[4] 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

Tiotropium

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.[8]

Tiotropium is 72% plasma protein-bound 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.[4]

Olodaterol

Olodaterol generally reaches maximum plasma concentrations within 10 to 20 minutes after inhalation. In healthy volunteers, the absolute bioavailability of olodaterol after inhalation was estimated to be approximately 30%, whereas the absolute bioavailability was less than 1% when the drug was given as an oral solution. Thus, the systemic availability of olodaterol after inhalation is primarily determined by lung absorption.[4]

Olodaterol exhibits multicompartmental disposition kinetics after both inhalation and intravenous (IV) administration. The volume of distribution is high (1,110 L/kg), suggesting extensive distribution into tissues. *In vitro* binding of [14C] olodaterol to human plasma proteins is approximately 60% and is independent of drug concentration.[4]

Metabolism and Elimination

Tiotropium

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.[4]

Olodaterol

Olodaterol is substantially metabolized by direct glucuronidation and by O-demethylation at the methoxy moiety, followed by conjugation. Of the six metabolites currently identified, only the unconjugated demethylation product binds to $beta_2$ receptors. This metabolite, however, is not detectable in plasma after chronic inhalation of the recommended therapeutic dose of tiotropium/olodaterol.

CYP2C8, 2C9, and 3A4 are involved in the O-demethylation of olodaterol, whereas the uridine diphosphate glycosyl transferase (UGT) isoforms UGT1A1, 1A7, 1A9, and 2B7 are involved in the formation of olodaterol glucuronides.[8]

Excretion

Tiotropium

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.[4]

Olodaterol

Total clearance of olodaterol in healthy volunteers is 872 mL/min, and renal clearance is 173 mL/min. The terminal half-life after IV administration is 22 hours. In contrast, the terminal half-life after inhalation is approximately 45 hours, indicating that the latter is determined by absorption rather than by elimination. The effective half-life of olodaterol at a daily dose of 5 mcg, calculated from the C_{max} in COPD patients, is 7.5 hours.[4]

After IV administration of [14C]-labeled olodaterol, 38% of the radioactive dose was recovered in urine and 53% was recovered in feces. The amount of unchanged olodaterol recovered in urine after IV administration was 19%. After oral administration, only 9% of olodaterol and/or its metabolites was recovered in urine, while the major portion (84%) was recovered in feces. More than 90% of the dose was excreted within five and six days after oral and IV administration, respectively. After inhalation, the excretion of unchanged olodaterol in urine within the dosing interval in healthy volunteers at steady state accounted for 5% to 7% of the dose.[4]

CLINICAL STUDIES

The efficacy of fixed-dose tiotropium/olodateral combinations is based primarily on two four-week dose-ranging trials in a total of 592 COPD patients and on two confirmatory, active-controlled, 52-week trials in a total of 5,162 COPD patients.[4]

Dose-Ranging Studies

Aalbers and colleagues conducted a four-week, randomized, double-blind, incomplete-crossover study to determine the optimum once-daily dose of olodaterol (5 and 10 mcg) and tiotropium (1.25, 2.5, and 5 mcg) in combination when delivered via the Respimat Soft Mist inhaler in patients with COPD. The study's primary efficacy endpoint was the trough forced expiratory volume in one second (FEV_1) response (the change from baseline) after four weeks of treatment (day 29). Secondary efficacy endpoints included the FEV_1 area under the curve from zero to six hours ($AUC_{0–6\ hrs}$) response after four weeks of treatment; the trough forced vital capacity (FVC) response, the FVC $AUC_{0–6\ hrs}$ response after four weeks of treatment; and the incidence and severity of adverse events.[9]

The study included male and female patients 40 years of age and older with a diagnosis of COPD confirmed by spirometric criteria. The patients were required to have a post-bronchodilator FEV_1 equal to or greater than 30% and less than 80% as well as a post-bronchodilator FEV_1/FVC ratio of less than 70%. Current and former smokers with a smoking history of more than 10 pack-years were also enrolled. Concomitant respiratory medications included inhaled corticosteroids, inhaled short-acting beta-adrenergics, LABAs, and short-acting anticholinergics.[9]

A total of 232 patients with COPD (133 men and 99 women) were enrolled and received treatment with study medication. At day 29, the adjusted mean trough FEV_1 and FEV_1 $AUC_{0–6\ hrs}$ were increased from baseline with olodaterol 5-mcg and 10-mcg monotherapy. The trough FEV_1 response and FEV_1 $AUC_{0–6\ hrs}$ responses were similar for olodaterol 5-mcg and 10-mcg monotherapy (0.071 L and 0.083 L, respectively, for trough FEV_1 response, and 0.188 L and 0.198 L, respectively, for FEV_1 $AUC_{0–6\ hrs}$ response).[9]

All of the tiotropium/olodaterol combinations (0/5, 1.25/5, 2.5/5, 5/5, 0/10, 1.25/10, 2.5/10, and 5/10 mcg) resulted in larger trough FEV_1 and FEV_1 $AUC_{0–6\ hrs}$ responses and higher FVC values compared with the respective olodaterol monotherapies.[9] The mean differences in trough FEV_1 for the tiotropium/olodaterol doses of 1.25/5, 2.5/5, and 5/5 mcg once daily from olodaterol 5 mcg were 0.54 L, 0.065 L, and 0.084 L, respectively.[4]

The authors concluded that the addition of tiotropium to olodaterol resulted in improvements in lung function parameters compared with olodaterol monotherapy in this four-week study.[9]

In another dose-ranging trial, Maltais and associates investigated the bronchodilator efficacy of a fixed-dose combination of tiotropium and olodaterol in comparison with tiotropium monotherapy, both administered using the Respimat Soft Mist inhaler, in 360 patients (196 men and 164 women; mean age, 63 years) with COPD. FEV_1 was measured pre-dose (trough) and for up to six hours post-dose.[10]

At the end of this randomized, double-blind, parallel-group study, the peak FEV_1 response from baseline was significantly increased for all doses of the tiotropium/olodaterol combination (5/2, 5/5, and 5/10 mcg) compared with tiotropium (5 mcg) alone.[10] The mean differences in trough FEV_1 for the tiotropium/olodaterol doses of 5/2, 5/5, and 5/10 mcg once daily from olodaterol 5 mcg were 0.24 L, 0.033 L, and 0.057 L, respectively.[4]

Confirmatory Studies

The positive results from the dose-ranging studies of fixed-dose tiotropium/

olodaterol combinations supported the evaluation of once-daily doses of tiotropium/olodaterol 2.5/5 mcg and 5/5 mcg in two 52-week, phase 3 confirmatory trials.[4,11] These replicate, randomized, double-blind, active-controlled, parallel-group studies evaluated a total of 5,162 COPD patients (1,029 receiving tiotropium/olodaterol 2.5/5 mcg or 5/5 mcg, 1,033 receiving tiotropium 2.5 mcg or 5 mcg, and 1,038 receiving olodaterol 5 mcg). All of the products were administered using the Respimat inhaler.[4,11] The primary endpoints of both studies were the change from baseline in FEV_1 $AUC_{0–3\ hrs}$ and trough FEV_1 after 24 weeks of treatment.[4]

Most of the 5,162 patients were men (73%) and were either white (71%) or Asian (25%), with a mean age of 64 years. The mean post-bronchodilator FEV_1 was 1.37 L, and the mean $beta_2$-agonist responsiveness was 16.6% of baseline (0.171 L). Pulmonary medications, such as inhaled steroids (47%) and xanthines (10%), were allowed as concomitant therapy.[4]

In both studies, the two fixed-dose combinations of tiotropium/olodaterol (2.5/5 mcg and 5/5 mcg) significantly improved FEV_1 $AUC_{0–3\ hrs}$ and trough FEV_1 compared with the individual components.

FEV_1 $AUC_{0–3\ hrs}$ responses for tiotropium/olodaterol (2.5/5 mcg and 5/5 mcg), for tiotropium (2.5 mcg and 5 mcg), and for olodaterol (5 mcg) were 241, 256, 148, 139, and 133 mL, respectively, in the first study, and 256, 268, 125, 165, and 136 mL, respectively, in the second study. In both trials, the improvements in the adjusted mean FEV_1 $AUC_{0–3\ hrs}$ with tiotropium/olodaterol (2.5/5 mcg and 5/5 mcg) versus those with the corresponding individual components were statistically significant ($P < 0.0001$) for all comparisons.[11]

Similarly, trough FEV_1 responses after 24 weeks for tiotropium/olodaterol (2.5/5 mcg and 5/5 mcg), for tiotropium (2.5 mcg and 5 mcg), and for olodaterol (5 mcg) were 111, 136, 83, 65, and 54 mL, respectively, in the first study, and 125, 145, 62, 96, and 57 mL, respectively, in the second study. The improvements with tiotropium/olodaterol 2.5/5 mcg and 5/5 mcg over the corresponding individual components were statistically significant ($P < 0.05$) in both studies.[11]

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

SAFETY PROFILE

Adverse Events in COPD Trials

The primary safety database for tiotropium/olodaterol 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.[4]

In these two clinical studies, 74.0% of the patients treated with tiotropium/olodaterol reported an adverse event, compared with 76.6% and 73.3% of the olodaterol and tiotropium groups, respectively. The most common adverse events were nasopharyngitis (12.4% for tiotropium/olodaterol, 11.7% for tiotropium, and 12.6% for olodaterol), cough (3.9%, 4.4%, and 3.0%), and back pain (3.6%, 1.8%, and 3.4%).[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.[4]

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.[4]

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/olodaterol is not indicated for the treatment of asthma.[4] Further, fixed-dose tiotropium/olodaterol is contraindicated in patients with a hypersensitiv-

ity to tiotropium, ipratropium, olodaterol, or any component of the product.[4]

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/olodaterol.[4]

Key Warnings and Precautions

Asthma-Related Death

Data from a large placebo-controlled study in asthma patients showed that long-acting beta$_2$-adrenergic agonists may increase the risk of asthma-related death. The increased risk of asthma-related death is considered a class effect of these agents, including olodaterol. No studies have been conducted to determine whether the rate of asthma-related death is increased in patients treated with tiotropium/olodaterol. As noted above, tiotropium/olodaterol is contraindicated in asthma patients.[4]

Deterioration of COPD and Acute Episodes

Treatment with tiotropium/olodaterol 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/olodaterol, health care providers should also prescribe an inhaled, short-acting beta$_2$ agonist in case rescue therapy is needed, and they should instruct patients on how and when to use it.[4]

Paradoxical Bronchospasm

As with other inhaled drugs containing beta$_2$-adrenergic agents, tiotropium/olodaterol may cause paradoxical bronchospasm, which may be life-threatening. If paradoxical bronchospasm occurs, tiotropium/olodaterol should be stopped immediately and an alternative therapy instituted.[4]

Cardiovascular Effects

Olodaterol, like other beta$_2$ 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/olodaterol 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.[4]

Worsening of Narrow-Angle Glaucoma

Tiotropium/olodaterol 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.[4]

Worsening of Urinary Retention

Tiotropium/olodaterol 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.[4]

Renal Impairment

Because tiotropium is mainly excreted via the kidneys, patients with moderate-to-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.[4]

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 beta$_2$-adrenergic agonists may increase plasma glucose levels.[4]

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. Olodaterol has not been investigated in patients whose diabetes mellitus is not well controlled.[4]

DOSAGE AND ADMINISTRATION

The recommended dose of tiotropium/olodaterol is two inhalations once daily at the same time of the day. Tiotropium/olodaterol should not be used at more than two inhalations every 24 hours.

Before the first use, the tiotropium/olodaterol 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/olodaterol should be monitored closely for anticholinergic effects.[4]

COST

The average wholesale price (AWP) of one tiotropium/olodaterol 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.[12]

P&T COMMITTEE CONSIDERATIONS

Because several drug classes are available for the treatment of COPD, many hospital pharmacies are questioning which of these agents should be on their institutions' formularies for inpatient use. Of the many drug classes used for COPD, LABAs and anticholinergics are the mainstays of current treatment protocols.[3] Both of these drug classes promote bronchodilation and improve airflow in COPD patients.

Fixed-dose tiotropium/olodaterol offers a long-acting beta$_2$ agonist in combination with a long-acting anticholinergic. Because of their extended activity, the two agents have an additive effect in maintaining airway dilation.[4] Since the approval of tiotropium bromide inhalation powder (Spiriva HandiHaler) and olodat-

erol (Striverdi Respimat), both marketed by Boehringer Ingelheim, the combined use of anticholinergics and LABAs has been widely incorporated into clinical practice and has been added to treatment guidelines for outpatient settings.[3]

It must be emphasized, however, that although tiotropium and olodaterol have been on the U.S. market for some time, they have not been widely used as a fixed-dose combination, and their long-term safety as a dual product has not yet been established. Current treatment recommendations for COPD exacerbations call for the use of short-acting agents, such as albuterol or ipratropium bromide.[13] Fixed-dose tiotropium/olodaterol is not approved for the treatment of acute exacerbations of COPD and would therefore be of limited use in acutely stressed hospitalized patients. Moreover, most COPD patients will probably bring their maintenance therapy to the hospital from home.

While of limited use in an inpatient setting, fixed-dose tiotropium/olodaterol has the potential to become a valuable option for outpatients. According to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines, long-acting anticholinergics and LABAs are the treatments of choice for GOLD classifications 2 through 4.[3] Therefore, tiotropium/olodaterol, a combination of both drug classes, is likely to provide optimal airway dilation. In addition, the product will probably appeal to patients because of its combination of two effective drug classes, and because it reduces the number of inhalers required for maintenance therapy.

Fixed-dose tiotropium/olodaterol is similar to umeclidinium/velanterol (Anoro Ellipta, GlaxoSmithKline)—another anticholinergic/LABA combination product (approved by the FDA in 2013). Tiotropium/olodaterol requires patients to inhale two puffs once daily, whereas umeclidinium/velanterol requires patients to inhale only one puff once daily. Despite this difference, tiotropium/olodaterol comes with 60 actuations compared with 30 actuations for umeclidinium/velanterol. Hence, the two medications are similar in terms of the length of treatment with each inhaler device.[14,15] Their costs are also the same: the AWP of an umeclidinium/velanterol inhaler, which should last for 30 days, is $379.[12,15] One advantage that tiotropium/olodaterol has over umeclidinium/velanterol is that it can be used in patients with an allergy to milk. Milk proteins are used during the manufacturing process of umeclidinium/velanterol; therefore, this medication cannot be used in patients who are allergic to milk. Further, umeclidinium/velanterol, which uses a dry-powder inhaler, requires patients to inhale with a long, steady, deep breath, which may be difficult for elderly patients. Tiotropium/olodaterol allows patients to inhale normally.[14,15]

CONCLUSION

The anticholinergic and LABA drug classes have been shown to decrease exacerbations and to improve respiration in patients with COPD. Tiotropium/olodaterol (Stiolto Respimat) is the newest combination drug product indicated for the maintenance of COPD.[16] Recent studies have demonstrated that the combination of tiotropium bromide and olodaterol hydrochloride is more effective at improving FEV_1 $AUC_{0–3\ hrs}$ than either of the two agents used alone.[11] Tiotropium/olodaterol is also one of the few combination products that includes a LABA and a long-acting anticholinergic. Like olodaterol alone, the fixed-dose combination of tiotropium and olodaterol improves airflow within five minutes after the first dose.[16] While the fixed-dose product has been associated with various adverse events, including nasopharyngitis, pneumonia, cough, and back pain, the proportions of patients who withdrew from clinical trials because of such events were significantly lower for the tiotropium/olodaterol combination than for tiotropium or olodaterol alone.[4] With these considerations in mind, fixed-dose tiotropium/olodaterol appears to offer an attractive option for the maintenance treatment of patients with COPD.

REFERENCES

1. Centers for Disease Control and Prevention. Chronic obstructive pulmonary disease (COPD). March 12, 2015. Available at: http://www.cdc.gov/copd/index.html. Accessed June 10, 2015.
2. Barnes PJ. Chronic obstructive pulmonary disease • 12: new treatments for COPD. *Thorax* 2003;58:803–808.
3. Global Initiative for Chronic Obstructive Lung Disease. Pocket guide to COPD diagnosis, management, and prevention: a guide for health care professionals. 2015. Available at: http://www.goldcopd.org/uploads/users/files/GOLD_Pocket_2015_Feb18.pdf. Accessed June 10, 2015.
4. Stiolto Respimat (tiotropium bromide/olodaterol inhalation spray) prescribing information. Ridgefield, Connecticut: Boehringer Ingelheim Pharmaceuticals, Inc.; June 2015. Available at: http://docs.boehringer-ingelheim.com/Prescribing%20Information/PIs/Stiolto%20Respimat/stiolto.pdf. Accessed October 15, 2015.
5. MedLibrary. Stiolto Respimat. June 25, 2015. Available at: http://medlibrary.org/lib/rx/meds/stiolto-respimat. Accessed November 4, 2015.
6. RxList. Stiolto Respimat. 2015. Available at: http://www.rxlist.com/stiolto-respimat-drug/indications-dosage.htm. Accessed June 13, 2015.
7. Micromedex. Tiotropium bromide. Available at: http://www.micromedexsolutions.com. Accessed June 13, 2015.
8. Micromedex. Olodaterol hydrochloride. Available at: http://www.micromedexsolutions.com. Accessed June 13, 2015.
9. Aalbers R, Maleki-Yazdi MR, Hamilton A, et al. Dose-finding study for tiotropium and olodaterol when administered in combination via the Respimat inhaler in patients with COPD [poster]. Presented at the European Respiratory Society Annual Congress; Vienna, Austria; September 1–5, 2012. Available at: http://www.boehringer-ingelheim.com/content/dam/internet/opu/com_EN/document/05_clinical_trials/P2882_Aalbers_Tiotropium_and_Olodaterol_ERS_2012_poster.pdf. Accessed November 4, 2015.
10. Maltais F, Beck E, Webster D, et al. Four weeks once daily treatment with tiotropium+olodaterol (BI 1744) fixed dose combination compared with tiotropium in COPD patients. *Eur Respir J* 2010,36:1014s [abstract 5557].
11. Buhl R, Maltais F, Abrahams R, et al. Tiotropium and olodaterol fixed-dose combination versus mono-components in COPD (GOLD 2–4). *Eur Respir J* 2015;45:969–979.
12. Red Book Online. Ann Arbor, Michigan: Truven Health Analytics. Accessed December 28, 2015.
13. Carrera M, Sala E, Cosio BG, et al. Hospital treatment of chronic obstructive pulmonary disease exacerbations: an evidence-based review. *Arch Bronconeumol* 2005;41:220–229.
14. Straight Healthcare. Inhaled anticholinergics. Available at: http://www.straighthealthcare.com/inhaled-anticholinergics.html#anoro-ellipta. Accessed June 24, 2015.
15. Anoro Ellipta (umeclidinium/vilanterol inhalation powder) prescribing information. Triangle Park, North Carolina: GlaxoSmithKline; May 2014. Available at: https://www.gsksource.com/pharma/content/dam/GlaxoSmithKline/US/en/Prescribing_Information/Anoro_Ellipta/pdf/ANORO-ELLIPTA-PI-MG.PDF. Accessed November 4, 2015.
16. Boehringer Ingelheim. FDA approves Boehringer Ingelheim's Stiolto Respimat as once-daily maintenance treatment for COPD. May 26, 2015. Available at: https://www.boehringer-ingelheim.com/news/news_releases/press_releases/2015/26_may_2015_copd.html. Accessed June 14, 2015. ■