Review Article

Exploring the Effect of Inhaled Indacaterol/Glycopyrronium in COPD Patients with Cardiovascular Changes

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ABSTRACT

Chronic obstructive pulmonary disease (COPD) is characterized by progressive airflow constraint and is highly prevalent disease which may cause functional disability. The use of dual bronchodilator plays major role in the management of chronic obstructive pulmonary disease. These combination drugs works by soothing the smooth muscles in the lungs. Both short acting and long acting bronchodilator combinations are very effective for moderate to severe COPD. Cardiovascular changes in patients with chronic obstructive pulmonary disease (COPD) with the use of these combination drugs are important for improving treatment decisions. Long-term safety, especially cardiovascular safety, is of particular interest in maintenance treatment of chronic obstructive pulmonary disease (COPD) with long acting β2-agonist and long acting muscarinic antagonist, given potential cardiovascular effect. Inhalers are most effective in managing respiratory disease, even though some have concern about the cardiovascular effect in long term therapy and inappropriate use of these drugs.

Keywords: COPD, bronchodilator, inhalers, combination, IND/GLY(Indacaterol/Glycopyrronium).

INTRODUCTION

The respiratory and cardiovascular systems are influenced by autonomic nervous system and are closely connected. Chronic obstructive pulmonary disease (COPD) largely preventable as well as manageable respiratory condition and is a leading cause of morbidity and mortality worldwide that leads a significant burden on society. It is the fourth leading cause of death and is directed to be the world's third leading cause of mortality by 2020. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines suggests the effectiveness of one or more bronchodilators as maintenance therapy for the treatment and management of COPD. [1]

Tobacco smoking is the main reason for COPD, which leads to lung inflammation that induces parenchymal tissue destruction, causes air trapping and airflow limitation. Therefore, it eventually raises many co morbidities, including cardiovascular diseases such as hypertension, ischemic heart disease (IHD), stroke, atrial fibrillation (AF), and heart failure (HF).[12]

Bronchodilators are the cornerstone of the pharmacological management of chronic obstructive pulmonary disease (COPD). The efficacy and safety of glycopyrronium and indacaterol, known as long-acting bronchodilator monotherapies in patients with moderate-to-severe COPD, has been estimated in several Phase III studies. In patients whose symptoms are inadequately controlled by bronchodilator monotherapy, the Global initiative for chronic Obstructive Lung Disease (GOLD) strategy for the management of COPD suggest the addition of a second bronchodilator; this is supported by data showing that the addition of a second bronchodilator from a different pharmacological class improves lung function, symptoms, and health status compared with monotherapy, without significantly increasing the risk of side effects. [2]

Indacaterol–glycopyrronium induced consequential lung deflation, normalised biventricular end diastolic volumes, and ameliorated cardiac filling in patients with COPD and pulmonary hyperinflation. The cardiac and pulmonary effects were more sizably voluminous than expected, and the data suggest that lung deflation can lead to direct cardiac amendments, manifested as a consequential increase in left ventricular end diastolic volume. This study is the first to show that lung deflation and amendment in cardiac filling translate to a clinically germane reduction of disease burden and dyspnoea. [4]

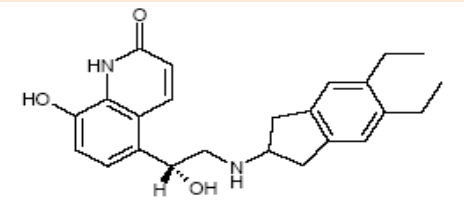
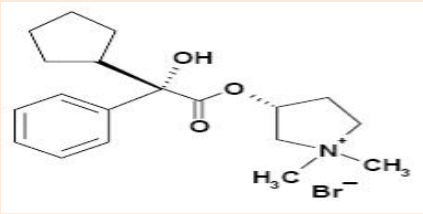
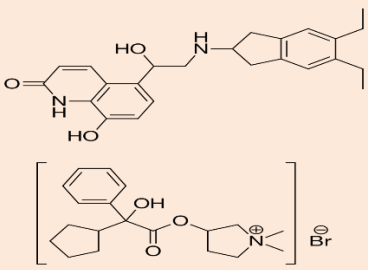
Cardiovascular changes with indacaterol/ glycopyrronium inhaled

The combination of a long-acting beta$_2$-agonist (indacaterol) and a long-acting muscarinic antagonist (glycopyrronium). Cardiovascular effects, such as cardiac arrhythmias, e.g., atrial fibrillation and tachycardia, may be seen following the administration of sympathomimetic agents and muscarinic receptor antagonists. In case such effects occur, then treatment may need to be ceased.

Table 1: Indacaterol, Inhaled/Glycopyrrolate Inhaled[6]

Classes	Dosage Forms & Strengths	Adverse Effects	Pharmacology
Anticholinergics Beta two agonist combination	ADULT inhalation powder (27.5mcg/15.6 mcg)/ capsule	Nasopharyngitis (4.1%) Hypertension (2%) Back pain (1.8%) Oropharyngeal pain (1.6%) **Post marketing Reports** Angioedema Dysphonia	**Glycopyrronium:** Long-acting muscarinic antagonist (LAMA); frequently referred to as an anticholinergic; produces broncho-dilation by inhibiting acetylcholine's effect on muscarinic receptors in the airway smooth muscle. **Indacaterol**: Long-acting beta2-agonist (LABA); stimulates intracellular adenyl cyclase, causing conversion of ATP to cyclic AMP; increased cyclic AMP levels cause relaxation of bronchial smooth muscle.

Table 2: Pharmaceutical Information

Chemical name:	Indacaterol maleate	Glycopyrronium bromide
Chemical name:	(R)-5-[2-(5,6-Diethylindan-2-ylamino)-1-hydroxyethyl]-8-hydroxy-1H-quinolin-2-one maleate	3-(2-Cyclopentyl-2-hydroxy-2-phenylacetoxy)- 1,1-dimethylpyrrolidinium bromide
Molecular formula and molecular mass	C24H28N2O3 • C4H4O4 (508.56)	C19H28NO3 Br Salt form on anhydrous basis: 398.33
Structural formula		
Physicochemical properties	Pure R-enantiomer Single polymorphic form, form A The pH of indacaterol maleate in 0.1% (g/100 ml) suspension in water at room Temperature is 4.9. The pH value of 0.1% (g/100 ml) solution in water/ethanol 80:20 (V/V) at room Temperature is 5.0. The melting range of indacaterol is 195 – 202°C with decomposition. Indacaterol maleate is a white to very slightly greyish or very slightly yellowish powder. Indacaterol maleate is freely soluble in N-methyl pyrrolidone and dimethylformamide, slightly soluble in methanol, ethanol, propylene glycol and polyethylene glycol 400, very slightly soluble in water, isopropyl alcohol and practically insoluble in 0.9% sodium chloride in water, ethyl acetate and n-octanol.	The drug substance glycopyrronium bromide presents 2 asymmetric carbon atoms and is an optically inactive racemic mixture of 2 stereoisomers (2S, 3R and 2R, 3S), hereafter referred to as the stereoisomer's (S, R) and (R, S). The pH of glycopyrronium bromide in 1.0% m/V (g/100 mL) solution in water at room temperature is 6.0. Melting range: 193 – 198 °C Glycopyrronium bromide is a white to to practically white Powder. Glycopyrronium bromide is freely soluble in water, 0.9% sodium chloride in water, methanol, ethanol (50% and 95%).
Indacaterol Glycopyrronium inhaled		

Cardiovascular effects such as tachycardia, arrhythmia, palpitations, myocardial ischemia, angina pectoris, hypertension or hypotension have been occured with use of with beta-adrenergic agonists. Along with that, beta-adrenergic agonists have been reported to change in electrocardiogram (ECG) reading, such as flattening of the T wave, prolongation of the QTc interval, and ST segment depression. So that, this inhaler like all products containing beta-adrenergic agonists, should be used with caution in patients with cardiovascular disorders, particularly coronary insufficiency, acute myocardial infarction, cardiac arrhythmias, and hypertension.

In a study they shows, the combination of glycopyrronium+indacaterol observed 5 mortalities among 339 subjects (4 in treatment and 1 in placebo group) without clinical evidence in ECG or vital sign changes during a 52-week study duration.[10,11]

Heart Rate

Like other beta$_2$-agonists, indacaterol can produce clinically significant cardiovascular effects in some patients as quantified by an increase in pulse rate, systolic or diastolic blood pressure or cardiac arrhythmias such as supraventricular tachycardia and extra systoles. If such effects occur, the utilisation of it may need to be discontinued.

QT Interval

Like other beta$_2$-agonists, caution is recommended if indacaterol/glycopyrronium is administered to patients with a known history of QTc prolongation, risk factors for torsade de pointes (e.g., hypokalemia), or patients who are taking medications known to perpetuate the QTc interval.[3]

Clinical findings

In healthy volunteers, single dose administration of indacaterol/glycopyrronium at up to a dose of 440/499.2 mcg was well-abode without clinically significant effects on the ECG, serum potassium or blood glucose. The potential signs and symptoms due to the over dosage of indacaterol/glycopyrronium are those of excessive beta-adrenergic stimulation and occurrence or exaggeration of any of the signs and symptoms, e.g., chest pain,hypertension or hypotension, tachycardia, with rates up to 200 bpm, arrhythmias, nervousness, headache, tremor, dry mouth, palpitation, muscle cramps, drowsiness dizziness, fatigue, malaise, hypokalemia, hyperglycemia, metabolic acidosis and insomnia. Like all inhaled sympathomimetic medications, cardiac arrest and even death may be associated with an overdose of this combination drug.

Safety and efficacy

The safety of drug assessed by checking all the treatment-emergent adverse event (AEs) and serious adverse events (SAE SAEs), monitoring vital signs (pulse rate, blood pressure) and analyzing laboratory parameters.[8] In some studies shows that lower respiratory tract infection occurred with higher frequency of IND+GLY administration. followed by COPD worsening, nasopharyngitis, cough, back pain.

Efficacy of IND+GLY assessed by performing spirometry, monitoring symptoms and health status. Spirometry measures FEV1, FVC, FEV1/FVC at each interval of time. The variation in the improvement of patient status before and after the administration of drug can easily monitored through spirometry analysis.

Symptoms status monitored by using Transitional Dyspnea Index (TDI), dairy-card data shows the improvement in the percentage of days able to perform activities by receiving the drug. In the assessment of health status, numerical difference in the St George Respiratory Questionnaire (SGRQ-C) total score is taken.[7]

CONCLUSION

In this review, we found that the combination of indacaterol/glycopyrronium used for chronic obstructive pulmonary disease was overall well tolerated with acceptable cardiac safety. This would contribute to the assessment of cardiovascular changes helpful to choosing best medicine in patients suffers chronic obstructive pulmonary disease (COPD) with cardiac abnormality.

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