Combination Therapy of Inhaled Indacaterol/Glycopyrronium for Chronic Obstructive Pulmonary Disease in the Very Elderly: Is It Safe? An Electrocardiographic Evaluation

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Keywords

Indacaterol/glycopyrronium · Chronic obstructive pulmonary disease · Elderly

Abstract

Cardiovascular (CV) comorbidities in patients with chronic obstructive pulmonary disease (COPD) are associated with increased morbidity and mortality, especially in old and very old subjects. The question if long-acting beta-agonist and long-acting muscarinic antagonist could be associated with the increased prevalence of CV-related adverse effects has puzzled, particularly in the past, specialists involved in the management of respiratory diseases. The safety of these compounds has scarcely been tested in patients aged ≥ 65 years with CV comorbidities, since randomized controlled trials rarely include this subpopulation. However, the fixed combination indacaterol/glycopyrronium has shown a favorable CV safety profile in both healthy volunteers and COPD patients. Thus, we aimed to assess the CV safety profile of the fixed combination indacaterol/glycopyrronium 110/50 μg in a series of COPD patients aged ≥ 80 years with

several comorbidities. Our results indicate that this combination is safe in the comorbid elderly, since no significant electrocardiographic abnormalities were recorded after the administration of the inhaled therapy. Only rare and non-clinically significant changes in heart rate and corrected QT interval duration were evident, mainly in females and in patients with concomitant impaired kidney function.

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Introduction

Chronic obstructive pulmonary disease (COPD) is a preventable and treatable disease characterized by a progressive decline in lung function, leading to high morbidity and mortality rates especially among the elderly [1]. It has been estimated that COPD will be the third cause of death worldwide by the year 2030. In the very elderly, COPD is often associated with several other comorbidities [2], mainly affecting the cardiovascular (CV) system, such as ischemic heart disease, heart failure and arrhythmias, cerebrovascular disease, and peripheral artery dis-

ease [3]. Concomitant heart failure is an independent predictor of mortality in patients with COPD exacerbations [4], given the strong relationship between heart and lung. Pharmacological strategies in COPD patients aim to reduce the number and frequency of exacerbations and improve symptom control and exercise tolerance. Long-acting muscarinic antagonists (LAMA) and/or long-acting β_2 -agonists (LABA), with or without inhaled corticosteroids (ICS), are the treatments of choice for the chronic management of COPD patients, according to the Global Strategy for Diagnosis, Management and Prevention of COPD (GOLD 2017) [1].

Noteworthy, in the past, both LAMA and LABA have been associated with adverse CV effects and increased CV mortality [5, 6]; however, newer and updated studies have, at least in part, reassured the safety of these compounds [7–9].

Despite some reassuring evidence, the CV safety of these drugs has not been well established in the very elderly, since only few retrospective data are available in people aged ≥ 65 years [10, 11]. For instance, very elderly patients are at an increased risk of developing conduction disturbances (i.e., QT prolongation, tachycardia and bradycardia, bundle branch block, and/or atrioventricular block), especially in the presence of comorbidities such as CV diseases or chronic kidney disease (CKD). This is further enhanced in the case of pharmacological treatments with multiple concomitant drugs for the management of comorbidities, due to possible interactions among molecules [12].

For these reasons, we assessed the CV safety of the indacaterol/glycopyrronium 110/50 μg combination in a population of very elderly COPD patients admitted to our Internal Medicine and Geriatrics Unit, by evaluating electrocardiographic alterations following a single dose of this LABA/LAMA combination.

Patients and Methods

A total of 30 COPD patients aged ≥ 80 years were recruited. They provided consent to the use of their data for research purposes, and the local Bioethics Committee approved this observation.

All the subjects evaluated had a history and/or a new diagnosis of COPD requiring inhaled bronchodilation with the indacaterol/glycopyrronium combination, according to the GOLD 2017 criteria [1].

Patients were either naive to inhaled bronchodilatation therapy, or they needed a switch to the indacaterol/glycopyrronium combination from their previous treatment strategies as per clinical indication.

Several exclusion criteria were applied: presence of a cardiac pacemaker, permanent atrial fibrillation (AFib), pre-existing left bundle branch block, history of long QT syndrome or evidence of corrected QT interval (QTc) duration >500 ms by the Fridericia formula [$\text{QTc} = \text{QT} / (\text{RR})^{0.33}$], and psycho-physical conditions precluding the proper administration of inhaled therapy (i.e., insufficient peak inspiratory flow, difficulties using the device).

Several additional parameters were analyzed for safety reasons: hemoglobin levels, creatinine (its plasma concentration was determined with the “Jaffé” method, and glomerular filtration rate was estimated with the CKD-EPI equation) [17], sodium, potassium, and calcium levels, and arterial blood gas analysis.

All patients had been admitted to our clinic for worsening of clinical status. All evaluations were obtained after stabilization of the acute illness conditioning the hospital admission. We recorded 3 long-stripe ECG lasting 30 s each, immediately before (T0) as well as 15 min (T1) and 60 min (T2) after the first administration of the indacaterol/glycopyrronium combination, according to the pharmacokinetic properties of the two drugs, which reach peak plasma concentrations (C_{max}) 15 min after inhalation [13]. ECG were evaluated for QTc duration, PR and QRS interval duration, heart rate (HR), and presence of arrhythmias or either supraventricular or ventricular ectopic beats.

Moreover, arterial blood pressure, HR, and pulse-oximetry were measured at the same time intervals.

Our group used the following definitions to classify patients: dyslipidemia = total cholesterol levels ≥ 200 mg/dL and/or use of lipid-lowering drugs; renal impairment = $\text{eGFR} < 60$ mL/min/ 1.73 m^2 ; anemia = hemoglobin < 12 g/dL; polypharmacotherapy = more than 5 concomitant drugs in each single patient.

Statistical Analysis

Statistical analysis was performed with the SPSS software (Version 13 for Windows; SPSS Inc., Chicago, IL, USA). Data were expressed as means $\pm$ standard deviation for normal distribution variables and as medians (interquartile range) for non-normal distributions. A p value < 0.05 was considered statistically significant.

Analysis of variance (ANOVA), analysis of co-variance (ANCOVA), McNeman test, Friedman test, and the two-sided test marginal homogeneity were used to assess the differences of the selected variables at the specified time intervals T0, T1, and T2.

Results

The baseline characteristics of the enrolled patients are shown in Table 1. A slight majority of patients were females (56.7%), with a mean age of 86.5 ± 4.6 years. The most frequently used CV drugs were beta-blockers (65.2%), ACE-inhibitors/ARBs (78.3%), diuretics (65.2%), digoxin (4.3%), lipid-lowering drugs (20.0%), and antiplatelet/antithrombotic agents (63.3%).

At T0, the mean systolic blood pressure was 121.6 ± 24.0 mm Hg, the mean diastolic blood pressure was 67.6 ± 13.4 mm Hg, and the mean HR was 76.7 ± 16.7 bpm.

Table 1. Baseline (T0) characteristics of the population

<i>Demographic variables</i>	
Age, years	86.5±4.6
Female gender	17 (56.7)
Smokers	25 (84)
Polypharmacotherapy	25 (83.3)
Type 2 diabetes mellitus	7 (23.3)
Dyslipidemia	11 (39.3)
Arterial hypertension	24 (80.0)
Anemia	13 (43.3)
Chronic kidney disease	9 (30)
Heart failure	17 (58.6)
Peripheral artery disease	17 (58.6)
Previous stroke/transient ischemic attack	5 (16.7)
Previous coronary artery disease	7 (24.1)
Paroxysmal AFib	12 (40.0)
<i>Laboratory parameters</i>	
Hb, g/dL	12.2±2.0
Creatinine, mg/dL	1.0±0.4
eGFR, mL/min/1.73 m ²	61.1±19.6
Sodium, mEq/L	139.7±3.8
Potassium, mEq/L	4.3±0.5
Calcium, mg/dL	8.8±0.8
<i>Arterial blood gas analysis</i>	
pH	7.45±0.04
pO ₂ , mm Hg	62.1±10.0
pCO ₂ , mm Hg	45.7±6.9
HCO ₃ ⁻ , mEq/L	31.2±4.5
SaO ₂ , %	94.7±2.8

Continuous variables are expressed as means ± standard deviation. Categorical variables are expressed as absolute numbers and percentages. AFib, atrial fibrillation; Hb, hemoglobin; eGFR, estimated glomerular filtration rate.

No variations in blood pressure levels and HR were noted over time (Fig. 1a, b).

All patients were in sinus rhythm at T0 and no arrhythmias were registered at both T1 and T2. The mean QTc interval duration was 428.9 ± 40.1 ms, the mean PR duration was 174.5 ± 39.6 ms, and the mean QRS duration was 100.3 ± 29.6 ms. The interval durations were constant over time (Fig. 2). At T1, 1 male and 1 female patient presented a transient prolongation of the QTc interval above normal reference values (QTc <450 ms for men and <470 ms for women), with values of 474 and 509 ms, respectively. In both cases, the QTc interval returned to normal values at T2, none of them had an increase of greater than 60 ms, and neither patient presented QTc prolongation after 60 min of indacaterol/glycopyrronium administration.

Single supraventricular or ventricular ectopic beats were present in 11 patients at T0; the prevalence of ectopic beats remained stable after indacaterol/glycopyrronium administration, with 9 and 10 patients showing 1 ectopic beat at T1 and T2, respectively. The administration of the LABA/LAMA combination therapy did not result in any new-onset arrhythmias.

We additionally analyzed the effects of several independent parameters on HR and QTc interval duration after administration of the combined inhalation therapy. The parameters evaluated were gender, anemic state, presence of heart failure signs and symptoms, CKD, paroxysmal AFib, and concomitant use of beta-blockers. Among females, a statistically significant reduction in HR at T2 versus T0 was documented ($p = 0.014$), whereas HR remained stable in males (Fig. 3). QTc duration was longer in females at T0 as compared to male patients ($p = 0.046$), but the difference disappeared at both T1 and T2 (Fig. 4).

A slight prolongation in the QTc interval duration was found in patients with CKD between T1 and T2 (Fig. 5), although not statistically significant.

Hematic concentrations of the main electrolytes analyzed (sodium, potassium, and calcium) did not appear to influence HR variability or QTc interval duration (all $p = \text{ns}$).

Discussion

An increasing number of elderly patients need hospitalization for COPD exacerbation, with 90-day mortality rates 3-fold higher than in younger patients [14]. The majority of these deaths are related to CV comorbidities in COPD patients [15]. Of note, recent studies from our group demonstrated the high prevalence of heart failure in very elderly patients admitted to hospital for COPD, as well as the important role of CV therapies in this subgroup of patients [16, 17]. However, these very high-risk populations are scarcely represented in randomized controlled trials, with scarce evidence available on the safety and tolerability of pharmacological therapies in this particular population [18].

The negative impact of COPD on the CV system may depend on several factors: the commonly shared risk factors, such as cigarette smoking, sedentary lifestyle, and the chronic proinflammatory state with subsequent microcirculation disturbances [19, 20].

LABA and LAMA represent the mainstay of inhaled bronchodilation therapy, with a strong positive impact

Fig. 1. Arterial blood pressure (BP) (a) and heart rate (b) variability after a single dose of indacaterol/glycopyrronium.

on quality of life and number of exacerbations [21]. In Italy, tiotropium, glycopyrronium, umeclidinium, and aclidinium are the approved LAMA for COPD chronic management, whereas vilanterol, indacaterol, olodaterol, formoterol, and salmeterol are the approved LABA. All these drugs can be used alone or in combinations, since the fixed compound combination exerts a synergic effect on patients' obstructed airways maximizing bronchodilation [22].

Although the population is aging and many elderly patients present with both COPD and CV comorbidities, scarce evidence is available regarding the safety of the newer LABA/LAMA combination drugs in this group of patients [22]. A large observational population-based study investigating patients with a mean age of 79.0 ± 7.1 years has recently revealed an increased CV-related hospitalization rate in patients treated with LABA and/or LAMA, independent from the pharmacological drug class used [6]. Other evidence points to a good safety profile of LABA/LAMA combination in COPD patients [9].

In our experience, we did not register significant variations in HR and QTc, PR, and QRS intervals from baseline to both 15 and 60 min after the administration of a single indacaterol/glycopyrronium 110/50 µg dose, in a population of very elderly with multiple comorbidities.

QT prolongation is a surrogate marker of proarrhythmic risk of non-anti-arrhythmic drugs; moreover, COPD exacerbations with respiratory failure are an independent predictor of arrhythmias [23, 24]. Of note, the increased prevalence of comorbidities in the elderly is linked to prolonged hospitalization and worse in-hospital mortality in patients aged >73 years [2]. In young healthy volunteers, glycopyrronium showed a very safe profile regarding QTc interval modifications, even at higher than therapeutical doses, compared with placebo [13]. Similar findings were also obtained in the GLOW1 study, in which none of the patients developed a QTc prolongation of >500 ms [25]. A recent paper on indacaterol safety in COPD patients aged ≥65 years [26] concluded that incidences of adverse events among indacaterol- or placebo-treated patients

Fig. 2. QTc (a), PR (b), and QRS (c) interval duration variability after a single dose of indacaterol/glycopyrronium.

were similar, regardless of the age group. Moreover, patients treated with the indacaterol/glycopyrronium combination in the SHINE study did not experience any CV event, without significant differences in QTC interval duration and AFib incidence versus both single pharmacological agents and placebo over a 26-week follow-up period [27].

We also evaluated the independent effect of several variables on the variability of HR and QTC interval dura-

tion: a slightly gender-related difference in HR was noted, although not statistically significant; regarding the QTc interval, only the presence of CKD might influence its duration, with a transient prolongation of the QTc interval at T1 and T2 in patients with versus patients without CKD. We do not know the true reason behind this finding, a causal effect was not proven, a possibility for a chance finding could be taken into account. At present, there are no requirements for dose adjustment or contra-

Fig. 3. Gender-dependent variability in heart rate.

Fig. 4. Gender-dependent QTc interval duration variability.

Fig. 5. Chronic kidney disease (CKD)-related QTc interval prolongation.

indications for indacaterol/glycopyrronium use in COPD patients with mild-to-moderate CKD or more than 75 years old.

Of note, we evaluated very old patients from a “real-life” setting, usually not represented in clinical trials. However, our analysis presents several limitations. First of all, a relatively low number of patients was observed. Secondly, the single ECG recordings at different times do not inform about rhythm alterations during prolonged periods, and thus 24-h ECG-Holter monitoring should be necessary.

Conclusion

The CV safety of LABA and LAMA and their combination is still debated. We showed that the indacaterol/glycopyrronium 110/50 µg combination is associated with a good cardiac safety profile in the very elderly with

multiple comorbidities, in terms of short-term proarrhythmic risk after a single dose of this compound combination.

Our data offer new insights on this issue, and further studies may in the future assess the CV safety profile of bronchodilation therapies in larger groups of elderly patients over the medium-long period.

Acknowledgement

The authors thank Luca Giacomelli, PhD, for providing medical writing on behalf of Content Ed Net; this assistance was funded by Novartis Farma SpA.

Financial Disclosure and Conflicts of Interest

The authors have no conflicts of interest directly relevant to this study.

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