The Respiratory “Overlap Syndrome”: Efficacy and Usefulness of the Combined Double Bronchodilation

Albino Petrone^a Filippo Luca Fimognari^b Francesco Mormile^d
Leonello Fuso^d Michela Quartieri^c Ludovico Petrone^e Francesco Romano^a

^aDepartment of Respiratory Diseases, Santa Barbara Hospital, Rogliano, Italy; ^bDivision of Geriatrics, Annunziata Hospital, Cosenza, Italy; ^cDepartment of Emergency Medicine, San Francesco Hospital, Paola, Italy; ^dDepartment of Respiratory Diseases, Catholic University of the Sacred Heart, Rome, Italy; ^eUniversity of Calabria, Rende, Italy

Keywords

Chronic obstructive pulmonary disease · Obstructive sleep apnea syndrome · Overlap syndrome · Indacaterol · Glycopyrronium · GOLD stage

Abstract

The coexistence of chronic obstructive pulmonary disease (COPD) and obstructive sleep apnea syndrome in a single patient is known as “overlap syndrome,” and worsens the prognosis of the affected subjects. A marked bronchodilation may be useful for the treatment of this condition. In fact, as stated in the GOLD 2017 guidelines, the combination of indacaterol/glycopyrronium may exert positive synergistic effects on smooth muscle cell and airway resistance, with a more pronounced efficiency in reducing lung hyperinflation. Noteworthy, inhaled bronchodilators favorably alter the dynamically determined components of resting lung hyperinflation and help deflate the overinflated lungs. This is particularly important in order to improve dyspnea, exercise performance, and night saturation, especially when combined with continuous positive airway pressure ventilation, as reported in our case series. We report 3 cases of patients with COPD in a stable clinical condition, referred to the De-

partment of Respiratory Pathophysiology at the “Mariano Santo” Hospital in Cosenza, due to possible symptoms suggestive of obstructive sleep apnea, and who were successfully treated with indacaterol/glycopyrronium at a fixed dose.

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Introduction

Chronic obstructive pulmonary disease (COPD) is currently the fourth leading cause of death in the world, projected to reach the third podium position by 2020. More than 3 million people have died from COPD, accounting for 6% of all deaths globally [1]. Obstructive sleep apnea (OSA) syndrome is a common disease that involves at least 4% of males and 2% of the female adult population. OSA is probably the most common respiratory disorder, with recent data from the United States and Europe reporting a rate between 14 and 49% of middle-aged men suffering from clinically relevant OSA [2, 3]. On an individual level, OSA leads to a significant decrease in quality of life and functional capacity, alongside a markedly increased risk of cardiovascular diseases and

death [2, 3]. A bulk of data also suggest that the presence and severity of OSA and associated nocturnal hypoxemia correlate with an increased risk of diabetes and cancer. OSA is characterized by recurrent episodes of upper airway obstruction during sleep, corresponding to recurrent cycles of desaturation and re-oxygenation, sympathetic overactivity, and intrathoracic pressure changes. All these features lead to sleep fragmentation and consequent daytime fatigue and sleepiness [4]. COPD and OSA syndrome represent 2 of the most prevalent chronic respiratory disorders in clinical practice, and their coexistence in the same patients is referred to as “overlap syndrome” [5].

Epidemiological studies indicate a prevalence of the overlap syndrome of approximately 1% in the population. In the Sleep Heart Health Study, a large community-based cohort study which included polysomnography and spirometry, 0.5% of the participants presented airflow obstruction. In a European study with predominantly mild COPD patients, OSA recurred in 3% [5, 6].

Nocturnal hypoxemia is one of the most important sleep abnormalities in COPD and OSA. The overlap syndrome causes more severe nocturnal hypoxemia than either disease alone [6, 7]. Daytime hypercapnia is also more common in overlap patients. Noteworthy, the more pronounced hypoxemia and hypercapnia might result in greater cardiovascular morbidity and mortality, as some evidence reported. Pulmonary hypertension is more prevalent in overlap patients, and a preliminary report indicates that overlap patients also suffer from higher mortality rates than patients with COPD alone [3, 7].

Inhaled bronchodilators are the main therapeutic agents for COPD. New agents such as indacaterol and glycopyrronium, with a prolonged duration of effects of up to 24 h, have recently been developed, providing new perspectives in the field of the once-a-day therapy in fixed combinations. Multiple evidence supports the mechanistic rationale, clinical efficacy, and safety of combining anticholinergic and β_2 -agonist bronchodilators [8, 9]. The rationale of using these classes of drugs is based on the high density of β_2 -adrenergic receptors available throughout the respiratory tree and on the key pathogenic role played by neurogenic cholinergic mechanisms in COPD.

The pharmacological characterization of the interaction between glycopyrronium bromide and indacaterol fumarate has shown that the coadministration of these two bronchodilators leads to a synergistic improvement of bronchodilation. Thus, by leveraging different receptor types at submaximal doses, this combination increases the therapeutic benefits while minimizing the dose-dependent side effects [10, 11].

We report 3 cases of patients with COPD in a stable clinical condition, referred to the Department of Respiratory Pathophysiology at the “Mariano Santo” Hospital in Cosenza, due to possible symptoms suggestive of OSA, and who were successfully treated with indacaterol and glycopyrronium at a fixed dose.

Case Description

Three patients complaining of symptoms suggestive of OSA came to our attention. These symptoms were unexplained daytime sleepiness, restless sleep, loud snoring, morning headaches, difficulties in concentrating, mood changes (irritability, anxiety, and depression), forgetfulness, increased urination and/or nocturia, and dyspnea on exertion. For all patients, the diagnosis of GOLD 2, B COPD dated 2 years and was indicated by another hospital, whose pneumonologists suggested starting long-acting muscarinic antagonist (LAMA) therapy with glycopyrronium.

A detailed clinical history was obtained and a physical examination was performed. Lung function testing consisted of spirometry, carried out according to the American Thoracic Society (ATS) guidelines; exercise tolerance was assessed with the six-minute walking test and modified Medical Research Council (mMRC) dyspnea scale. All patients and control subjects underwent a full-night cardiorespiratory study (Vitalnight, Vitalaire – Airliquide Healthcare); thoracoabdominal movements were detected by inductance plethysmography, arterial oxygen saturation (SaO_2) was measured by a finger probe oximeter, and nasal flow was measured by nasal cannulas and pressure transducer. Respiratory events were manually scored. Additionally, subjective somnolence was evaluated in all participants by the Epworth Sleepiness Scale (ESS). Morning arterial blood gas concentrations were determined (ABL 520, Radiometer, Copenhagen), and a standard spirometry was performed. The ratio between the forced expiratory volume in the first second and the forced vital capacity (FEV_1/FVC) was considered indicative of airway obstruction if $<70\%$ (Table 1). All patients were diagnosed with OSA syndrome and referred to continuous positive airway pressure therapy and daily oxygen therapy.

Four months after treatment initiation, patients' compliance was objectively measured with a machine time counter. Moreover, all patients were re-administered the ESS questionnaire and their respiratory function was re-evaluated. A second full-night cardiorespiratory study was performed during ventilation therapy.

Polysomnographic data showed an improvement of lung function at night, although nocturnal desaturation analyses were still prolonged (see Table 2 for details).

All patients indicated remarkable improvements from their subjective perspective of daytime and nighttime symptoms, including night snoring, daytime sleepiness, nocturia, concentration, and mood changes. Conversely, dyspnea on exertion still persisted, as demonstrated also from the improvement in meters walked at the walking test (Table 2). A repeat spirometry indicated persisting pulmonary obstruction, with an increased Motley index (residual volume to total lung capacity ratio, %), expressing dynamic hyperinflation [12].

The recent GOLD 2017 guidelines suggest treating COPD patients with persisting airflow limitation with the long-acting β_2 -

Table 1. Baseline characteristics of the 3 patients with overlap syndrome in our case series

Gender (male/female), <i>n</i>	2/1
Age, years	66.3±1.52
BMI	30.8±0.5
ESS score	10±1
PaO ₂ , mm Hg	74.2±4.7
PaCO ₂ , mm Hg	40.8±3.6
pH	7.41±0.02
FEV ₁ , L	2.02±0.19
FVC, L	3.14±0.27
FEV ₁ /FVC	64.1±1.8
RV/TLC, % predicted	137.8±1.53
AHI, events/h	42.7±4.5
Mean SaO ₂ , %	91.3±1.0
T <90, %	31.06±0.51
Walking test, m	350±10
mMRC (dyspnea scale)	1.6±0.5

Values are means ± SD if not otherwise stated.

agonist (LABA) plus LAMA combination, especially in cases where a single long-acting bronchodilator (LABA or LAMA) did not provide adequate control of respiratory symptoms. Thus, we switched our patients to the indacaterol/glycopyrronium combination therapy [13]. Three months after therapy modification, our patients were re-evaluated for lung function by means of spirometry, walking test, and mMRC dyspnea scale. Overnight respiratory function was also checked by nocturnal pulse oximetry testing during continuous positive airway pressure ventilation without oxygen addition. The results showed improvements in the Motley index (reducing air trapping), walking test, and mMRC dyspnea scale (Table 2). Thus, therapy was confirmed with further suspension of oxygen administration during the ventilator support.

Discussion

Synergistic effects of indacaterol and glycopyrronium are responsible for their dual action, based on reciprocal potentiation resulting in a maximization of bronchodilation [14]. Laboratory studies suggest that synergistic effects may occur between LABA and LAMA by a variety of mechanisms. For example, β_2 -adrenoceptor agonists can activate prejunctional β_2 -adrenoceptors to reduce acetylcholine release, and inhibitory crosstalk may exist between M3 receptors and β_2 -adrenoceptors in airway smooth muscle cells. Bronchodilators reduce airway smooth muscle tone and resistance, improve airflow, and accelerate the mechanical time constants for lung emptying [14, 15]. In this way, inhaled bronchodilators favorably alter the dynamically determined components of

Table 2. Clinical features of the 3 patients after the initiation of continuous positive airway pressure ventilation (CPAP) and after the addition of indacaterol/glycopyrronium (I/G) combination therapy to their therapeutic management strategy

	Baseline	With CPAP	With I/G combination therapy
FEV ₁ , L	2.02±0.19	2.01±0.26	2.23±0.30
FVC, L	3.14±0.27	3.27±0.34	3.43±0.31
FEV ₁ /FVC	64.1±1.8	64.2±3.8	64.8±3.8
RV/TLC, % predicted	137.8±1.53	128.7±1.27	116.4±1.96
SaO ₂ , %	91.3±1.0	94.2±0.85	4.5±0.3
T <90, %	31.06±0.51	18.5±1.25	6.3±1.0
Walking test, m	350±10	375±0.4	395±5
mMRC (dyspnea scale)	1.6±0.5	1.33±0.85	0.33±0.47
CPAP duration, h		5.9±0.3	5.86±0.4

Values are means ± SD.

resting lung hyperinflation and help deflate the overinflated lungs. Moreover, the combination of LAMA and LABA can have additive effects on reducing lung hyperinflation [10, 15].

The Sleep Heart Health Study demonstrated that patients with both OSA and COPD are at a greater risk of prolonged oxygen desaturation at night than patients with only OSA; this more prolonged hypoxemia, or even the coexistence of COPD, appears to considerably increase morbidity and mortality, as compared to OSA alone. There is also increasing evidence that both COPD and OSA may have systemic consequences [16, 17]. Both conditions cause inflammation via various mediators (tumor necrosis factor alpha, interleukin-6, and interleukin-8), in addition to the oxidative stress they create [16]. An excellent review by McNicholas [3] highlights the similar mechanisms through which these diseases may lead to cardiovascular comorbidities [18].

Conclusion

Our aim in presenting this case series was to highlight the complexity of treating patients with overlap syndrome, in which the focus on symptoms and pulmonary functional parameters both at daytime and at night can prevent improper and costly therapy. In our report, we maximized bronchodilation with the association indacaterol/glycopyrronium, thus resolving persistent hyper-

inflation and being able to stop oxygen administration. Effective and sustained bronchodilation is a key strategy for improving dyspnea and exercise performance, and it can also improve nocturnal respiratory capabilities by improving night saturation.

Our limited clinical experience should be regarded with interest in the light of new clinical randomized controlled studies, in order to improve our knowledge of the overlap syndrome and thus allowing clinicians to find the right balance between ventilation and bronchodilator therapy in these patients.

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 paper.

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