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Cent. Eur. J. Med. • 6(1) • 2010 • 26-30
DOI: 10.2478/s11536-010-0053-2

Central European Journal of **Medicine**

LABA in patients with stage I COPD and mild sleep apnea syndrome: a pilot study

Research Article

Ivan Kopitovic, Marija Kojicic, Mirjana Jovancevic Drvenica, Miroslav Ilic

Institute for Pulmonary Diseases of Vojvodina, 21204 Sremska Kamenica, Serbia

Received 17 August 2010; Accepted 20 August 2010

Abstract: Patients suffering from both sleep apnea-hypopnea syndrome (SAHS) and chronic obstructive pulmonary disease (COPD) have a more severe form of sleep apnea. Knowing all pathophysiological aspects that mutually interact in sleep disorders and COPD, we aimed to investigate if the introduction of long-acting ß2 agonists (LABA) during the night could improve overnight oxygenation and the ability to perform daily activities in stage I COPD patients with mild SAHS. We conducted a prospective study of 22 patients with stage I COPD and SAHS confirmed by overnight polygraph screening, without nocturnal CPAP treatment. During twelve weeks, all patients used LABA (salmeterol 50 mcg) with a metered dose inhaler before bedtime. The levels of apnea hypopnea index, oxygen saturation, heart rate, and Epworth daytime sleepiness scale (ESS) were recorded before and after the treatment. There was a significant improvement of lowest and average overnight oxygenation compared to baseline (mean difference 2.1±0.42, $p<0.0001$; 1.7±0.3, $p<0.0001$, respectively). In addition, patients reported reduction in daytime sleepiness according to ESS (mean difference 1.23±0.51; $p=0.03$). Fewer patients exhibited tachycardia when on salmeterol (68 vs. 41%; $p=0.01$). Use of inhaled salmeterol improves overnight oxygenation in patients with stage I COPD and SAHS. Future prospective studies are warranted to confirm this potentially beneficial effect of long-acting ß2 agonists.

Keywords: *COPD • Night hypoxemia • Sleep apnea • Adrenergic beta-agonists • Polygraphy*

1. Introduction

Both chronic obstructive pulmonary disease (COPD) and sleep apnea/hypopnea syndrome (SAHS) are chronic progressive diseases [1,2]. SAHS is reported in 10–15% of COPD patients [3]. A combination of these two disorders (overlap syndrome-OS) is present in about 0.5% of the adult population >40 years [4], but the prevalence of OS in asymptomatic patients is probably underestimated [5]. Patients suffering from overlap syndrome are at increased risk of nocturnal hypoxemia, and consequently pulmonary hypertension and right heart failure, compared with those with COPD or SAHS alone [6,7]. In addition, these patients have higher mortality rates compared with SAHS patients alone [8].

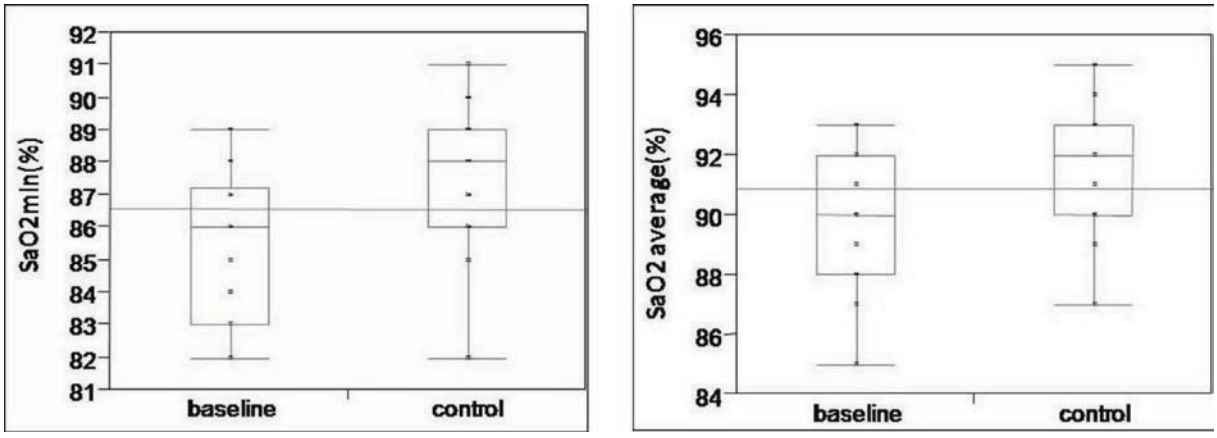
While the pathophysiologic interactions of these two disorders largely remain unclear [9], recent studies have indicated that the systemic inflammation present in both COPD and SAHS may play an important role in the development of the cardiovascular complications that are often seen in these patients [10]. Continuous positive airway pressure (CPAP) treatment in patients with OS has been shown to reduce the risk of cardiac comorbidities, but the data is limited to patients with severe forms of both COPD and sleep apnea.

Possible mechanisms of respiratory disorders during sleep include hypoventilation, ventilation/perfusion mismatches, altered respiratory muscles contractions, reduced mucociliary clearance, and increased inflammation [3,11]. In addition, cholinergic tone is increased at night, favoring bronchoconstriction [12]. The beneficial effects of long acting ß2 agonists (LABA) on nighttime lung function and patient perceptions of sleep have been demonstrated in asthma patients [13], but no data are available for COPD patients.

Since patients with OS are more likely to develop more severe hypoxemia during sleep, thus promoting the chronic complications of these two disorders, and considering the pharmacological effects of long acting ß2 agonists, we reasoned that the use of long acting ß2

* *E-mail: ikopitovic@gmail.com*

Figure 1. Effects of salmeterol on:



a) minimum overnight oxygenation
b) average overnight oxygenation

agonists can improve nocturnal hypoxemia in patients with OS early on the course of disease (combined stage I COPD and mild forms of SAHS).

2. Material and Methods

This was a prospective study of patients with mild COPD, using only short acting inhaled bronchodilator as needed, seen at the sleep center of the Institute for Pulmonary Diseases of Vojvodina, Sremska Kamenica, Serbia in 2007. All patients had clinical symptoms of sleep apnea (witnessed breaks in breathing, snoring, sudden awakenings or daytime sleepiness including falling asleep at inappropriate times). The patients underwent overnight polygraphic screening using BREAS SC 20 (Breas Medical AB, Mölnlyke, Sweden) and all had confirmed mild sleep apnea (AHI-apnea and hypopnea per hour of sleep index 5-15)[14] and oxygen desaturation episodes (SaO2 <90%).

During 12 weeks period, all patients used long-acting ß2 agonists (salmeterol 50 mcg) with the metered dose inhaler before bedtime. The polygraphic measurements were performed in all patients after 12 weeks of treatment. The levels of apnea hypopnea index, oxygen saturation and heart rate, as well as Epworth daytime sleepiness scale, were recorded before and after the treatment. All patients had confirmed stage I COPD according to the GOLD criteria (FEV1/FVC ≤70% and FEV1 ≥80%)[1] before initial treatment and had evidence of adequate oxygenation (PaO2 >60 mmHg) during wakefulness. Informed consent was obtained from each study participant with ethics approval for this study from Ethic Committee of Institute for Pulmonary Diseases of Vojvodina.

Exclusion criteria were: Apnea-hypopnea index ≥15; major comorbidities including coronary heart disease, heart failure, severe arrhythmias, diabetes, cerebrovascular diseases, hypercholesterolemia and history of psychiatric illness; use of continuous positive airway pressure ventilation (CPAP) or any sleep aid; known allergy to inhaled beta2 agonists; pregnant or lactating; inability or unwillingness to provide informed consent; inability to effectively use study medication or perform baseline measurements.

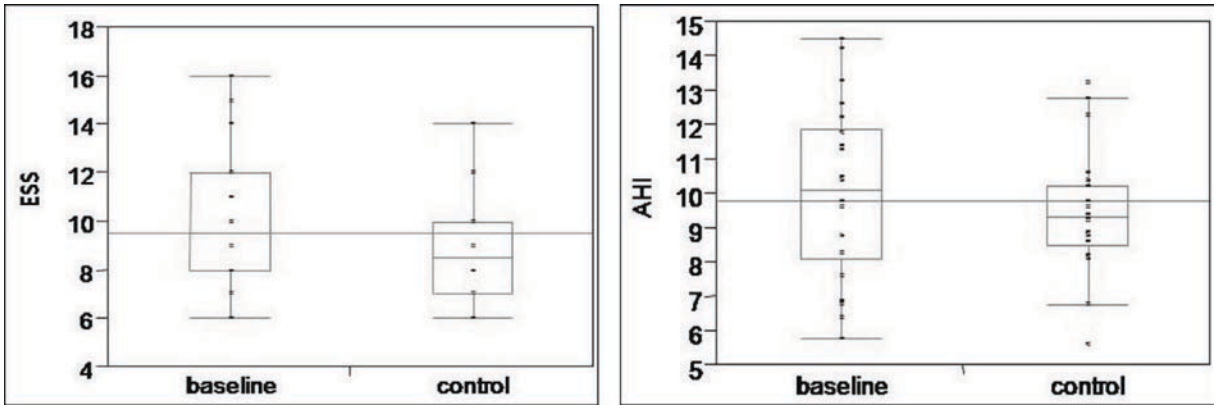
2.1. Statistical analysis

The continuous data are presented as mean (SD) and median (interquartile range (IQR)), and categorical as counts and percentages. The comparison of variables before and after the treatment was done using paired t test and McNemair test. The results were considered statistically significant at $p<0.05$. All data were analyzed using JMP statistical software (Version 8.0, Cary, NC).

3. Results

The study included 22 patients, 15 men (68%), median age 45 years (IQR 37–54). The median BMI was 29 (26–31). The baseline median Epworth scale was 10 (IQR 8–12). Following a twelve-week period, the results of a pulmonary function test showed no significant improvement and arterial blood gas analysis remained within normal reference range. No change in BMI was recorded. There was no difference in AHI ($p>0.05$) before and after the treatment. The values of lowest and average overnight oxygenation were significantly improved compared with baseline (mean difference 2.1±0.42, $p<0.0001$; 1.7±0.3, $p<0.0001$ respectively).

Figure 2. Effects of salmeterol on:



a) Epworth sleeping scale (ESS)
b) Apnea/hypopnea index (AHI)

Table 1. Patients' characteristic before and after twelve weeks administration of salmeterol.

	Before N=22	After N=22	p†
Epworth scale median (IQR)	10 (8, 12)	9 (7, 10)	0.03
AHImedian (IQR)	10 (8, 12)	9 (8, 10)	0.3
SaO_2 minmedian (IQR)	86 (83, 87)	88 (86, 89)	<0.0001
SaO_2 averagemedian (IQR)	90 (88, 92)	92 (90, 93)	<0.0001
Tachycardia (>100bpm), n (%)	15 (68)	9 (41)	0.01

†Paired analysis (t test, Mc Nemair)

(Figure 1) (Table 1) In addition, patients reported reduction in daytime sleepiness according to Epworth sleeping scale (mean difference 1.23±0.51; p=0.03). (Figure 2) Fewer patients exhibited tachycardia when on salmeterol (68 vs. 41%; p=0.01).

4. Discussion

The results of the present study show the beneficial effects of introducing bedtime long-acting beta agonists in patients with stage one COPD and mild sleep apnea syndrome. Improvement was recorded in both overnight oximetry measurements and self-reported severity of symptoms.

Following twelve weeks of bedtime salmeterol, there was a significant increase of lowest and average overnight oxygenation, but no improvements in levels of AHI were recorded. Nocturnal oxyhemoglobin desaturation develops in COPD, independent of the apnea/hypopnea level [10]. In the absence of SAH, the risk of nocturnal oxyhemoglobin desaturation increases at levels of FEV1/FVC below 65% [15]. The nocturnal desaturations are more severe in the overlap syndrome, thus predisposing to polycythemia, pulmonary hypertension and cor pulmonale [7,10]. In addition, these patients are shown to have an elevated economic burden compared with patients with COPD alone [16].

As expected, use of long-acting beta-2 agonist did not significantly improve PFT results or daytime symptoms of mild COPD. The current guidelines on COPD management do not recommend use of long-acting beta agonists early in the course of the disease [1]. Taking into account the additive effect of COPD and SAHS on nocturnal oxygen desaturation, and the fact that both disorders have a tendency to deteriorate over years, one should consider early therapeutic strategies in mild forms of OS. Previous studies have reported benefits of CPAP treatment for mild SAHS in terms of daytime function, but unacceptability of the CPAP has been reported in many such patients [17]. Other reports on CPAP use in patients with mild obstructive sleep apnea (OSA) demonstrated an advantage of CPAP over a placebo in general symptoms of OSA, but with no improvements in objective measurements of sleepiness [18]. In our study, all patients had good compliance and reported reduction in daytime sleepiness according to the ESS. Several mechanisms have been proposed to influence sleep disturbances in COPD patients, including hypoventilation, ventilation/perfusion mismatches, altered respiratory muscles contractions, reduced mucociliary clearance and increased inflammation [3,11].

During sleep, reduced intercostal muscle activity causes a decrease of functional residual capacity (FRC) and promotes ventilation perfusion mismatches in patients with chronic lung diseases [19,20]. These changes may be more severe in patients with lung hyperinflation resulting from the decreased amplitude of diaphragm excursions. Salmeterol has been previously shown to reduce hyperinflation in COPD patients [21]. In addition, β2-adrenoreceptor agonists

have antiinflammatory effects [22,23] and can improve mucociliary function in both normal and experimentally impaired airways [24]. Because of increased cholinergic tone, increased nocturnal airway resistance is seen even in normal subjects [25]. Salmeterol has been shown to decrease nocturnal bronchoconstriction and to improve sleep quality in asthma patients [26].

The limitations of our study are inherent in the small number of patients and a potential selection bias associated with recruitment of individuals who were referred to pulmonary and sleep clinics. In addition, full polysomnography was not performed, so the effects on sleep architecture could not be examined. While the safety of long-acting β2-agonists in OSA has previously been described [27], to our knowledge this is the first study to investigate effects of long-acting beta agonists in patients with mild COPD and SAHS, a group of patients that often remains underdiagnosed and undertreated despite the evidence of progressive nature of both diseases. In addition, patients with poor compliance to CPAP treatment may benefit from inhaled medication therapy.

In conclusion, use of inhaled salmeterol improves overnight oxygenation in patients with stage I COPD and SAHS. Future prospective studies are warranted to confirm this potentially beneficial effect of long-acting ß2 agonists and other bronchodilators, early in the course of the disease or in the case of poor compliance with CPAP therapy.

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