Effects of Salmeterol on Sleeping Oxygen Saturation in Chronic Obstructive Pulmonary Disease

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Key Words

Chronic obstructive pulmonary disease • Long-acting β -agonists • Oxygen saturation • Salmeterol • Sleep

Abstract

Background: Sleep is associated with important adverse effects in patients with chronic obstructive pulmonary disease (COPD), such as disturbed sleep quality and gas exchange, including hypoxemia and hypercapnia. The effects of inhaled long-acting β_2 -agonist therapy (LABA) on these disturbances are unclear. **Objectives:** The aim of the study was to assess the effect of inhaled salmeterol on nocturnal sleeping arterial oxygen saturation (SaO_2) and sleep quality. **Methods:** In a randomized, double-blind, placebo-controlled, crossover study of moderate/severe stable COPD patients, we compared the effects of 4 weeks of treatment with salmeterol 50 μg b.d. and matching placebo on sleeping SaO_2 and sleep quality. Overnight polysomnography (PSG) was performed at baseline, and after 4 and 8 weeks in addition to detailed pulmonary function testing. Of 15 patients included, 12 completed the trial (median age 69 years, forced expiratory volume in 1 s, FEV_1 : 39%). **Results:** Both mean SaO_2 [salmeterol vs. placebo: 92.9% (91.2, 94.7) vs. 91.0% (88.9, 94.8); $p = 0.016$] and the percentage of sleep spent below

90% of SaO_2 [1.8% (0.0, 10.8) vs. 25.6% (0.5, 53.5); $p = 0.005$] improved significantly with salmeterol. Sleep quality was similar with both salmeterol and placebo on PSG. Static lung volumes, particularly trapped gas volume, tended to improve with salmeterol. **Conclusion:** We conclude that inhaled LABA therapy improves sleeping SaO_2 without significant change in sleep quality. Copyright © 2009 S. Karger AG, Basel

Introduction

Chronic obstructive pulmonary disease (COPD) is characterized by progressive airflow limitation that is not fully reversible and is a leading cause of morbidity and mortality worldwide [1]. Sleep can be associated with clinically important adverse effects in patients with COPD, such as disordered gas exchange and disturbances in sleep quality [2]. Hypoventilation, a normal feature during sleep, has a disproportionate effect on hypoxemic patients because of their position on the oxyhemoglobin dissociation curve, leading to significant nocturnal desaturation, even in patients with mild awake hypoxemia [3]. In addition, the physiological reductions in accessory muscle contribution to breathing during sleep result in a

Fig. 1. Flow chart of study assessments. ABG = Arterial blood gas measurement; CXR = chest X-ray

decreased functional residual capacity (FRC), which leads to worsening ventilation-perfusion relationships and also aggravates hypoxemia [4]. Sleep-related hypoxemia may predispose to pulmonary hypertension, cardiac arrhythmias during sleep and nocturnal death during exacerbations [5–7].

Hypoxemia during sleep is easily corrected by supplemental oxygen, although this may not lead to improved sleep quality [8–10]. Pharmacological therapies which ameliorate some of the factors contributing to hypoxemia during sleep described above might be an alternative approach, and previous reports from our unit identified an improvement in nocturnal oxygen saturation, but not sleep quality, with the addition of theophylline [11] as well as with the long-acting anticholinergic agent tiotropium [12].

Long-acting β -agonists (LABA) are a recommended part of care in patients with moderate/severe COPD [1], but their effect on nocturnal oxygen saturation and sleep quality is unknown. Previous studies have shown that the addition of the LABA salmeterol results in a decrease in the exacerbation rate, improved health status, an increase in forced expiratory volume in 1 s (FEV_1) and in a reduction of lung hyperinflation at rest and during exercise [13–18].

We conducted a randomized, double-blind, placebo-controlled, crossover study to assess the effect of inhaled salmeterol on nocturnal sleeping arterial oxygen satura-

tion (SpO_2) and sleep quality. Primary outcome variables were the percentage of total sleep time spent below 90% of SpO_2 (TST90) and the mean SpO_2 during sleep.

Patients and Methods

Subjects

Subjects included clinically stable patients ≥ 40 years old with a diagnosis of COPD; a cigarette smoking history ≥ 10 pack-years; a $FEV_1 \leq 65\%$ of predicted, and a FEV_1 /forced vital capacity ratio $\leq 70\%$, in addition to an awake arterial oxygen tension (PaO_2) ≤ 9.98 kPa (75 mm Hg) prior to study entry. Patients were excluded if they were receiving regular oxygen therapy, had a clinically significant recent or concomitant disease other than COPD, or evidence of sleep apnea on baseline sleep studies (≥ 10 apneas or hypopneas per hour of sleep). Additional exclusion criteria included: evidence of asthma or atopy; respiratory infection in the preceding 6 weeks; concurrent use of inhaled corticosteroids $>1,500$ μ g daily or oral corticosteroids >10 mg daily. Concurrent treatment with inhaled salbutamol as required and inhaled tiotropium was permitted.

Study Design

This was a randomized, double-blind, placebo-controlled, crossover study, which was approved by the St. Vincent's University Hospital Ethics Committee. All subjects gave written informed consent. A flow chart of study assessments is given in figure 1. Each subject spent 3 nights in the sleep laboratory: the baseline night (before randomization), the 4-week night after the first study arm and the end-of-study night (8 weeks after randomization). One week before the baseline visit, patients stopped tak-

Table 1. Baseline characteristics of the entire study population and separately of all subjects included in the final analysis

Parameter	Patients included in study (n = 15)	Patients completed study (n = 12)
Male sex, n	8 (53%)	6 (50%)
Age, years	69 [62, 73]	69 [59, 73]
BMI	23.8 [21.6, 27.0]	23.2 [20.3, 28.1]
Smoking history, pack-years	38 [30, 50]	43 [30, 51]
Current smokers, n	1 (6.7%)	1 (8.3%)
FVC, liters	2.05 [1.78, 2.68]	1.97 [1.78, 2.45]
FEV ₁ , liters	0.96 [0.80, 1.10]	0.91 [0.79, 0.98]
FEV ₁ , % of predicted	41 [32, 46]	39 [31, 46]
FEV ₁ /FVC	38.2 [33.3, 54.4]	38.2 [35.4, 52.3]
PaO ₂ , kPa	9.1 [8.0, 9.9]	9.1 [8.0, 9.9]
PaCO ₂ , kPa	5.8 [5.3, 6.3]	5.9 [5.3, 6.3]
ESS	5 [2, 6]	5 [2, 6]
Medication prior to study		
LABA	15 (100%)	12 (100%)
Tiotropium	6 (40%)	5 (42%)
Inhaled steroid	13 (87%)	10 (83%)
Oral steroid	4 (27%)	3 (25%)

Values represent medians [interquartile ranges] unless otherwise stated. BMI = Body mass index; FVC = forced vital capacity; PaO₂/PaCO₂ = arterial oxygen/carbon dioxide tension.

ing regular LABA, if already on this medication. At baseline, each subject underwent detailed clinical assessment, testing for full blood count, liver and kidney function, arterial blood gas measurements (after at least 30 min of rest in the supine position) and a chest X-ray. Polysomnography (PSG) and detailed pulmonary function tests (PFTs; described below) were performed, and the subject's technique in using a DiskusTM inhaler was assessed by a respiratory specialist nurse. Subjects who met the inclusion criteria were randomized to either salmeterol 50 µg twice daily or placebo via a Diskus inhaler. After each study arm, subjects underwent PSG and PFTs, and were asked to fill out the SF-36 (Short Form-36 quality of life questionnaire) [19] and the Epworth Sleepiness Scale (ESS) [20]. During the whole study period, patients recorded their daytime alertness, perception of sleep quality, respiratory symptoms, number of puffs of rescue salbutamol and compliance with trial medication in a daily diary.

Procedures

Overnight PSG was performed on an automated system (SleepLab; Viaysis, Wurzburg, Germany) as previously described [21] and manually analyzed according to the criteria of Rechtschaffen and Kales [22].

Spirometry was performed with the patient seated and the best of three efforts recorded, and repeated 20 min after inhalation of 400 µg of salbutamol. Single-breath carbon monoxide diffusing capacity, in addition to static lung volumes by both multi-breath helium dilution and whole-body plethysmography, were also

Table 2. Oxymetry variables before and during total sleep time between salmeterol and placebo (n = 12) groups

Parameter	Salmeterol	Placebo	p value
SaO ₂			
Before sleep	95.0 [93.3, 95.8]	94.5 [92.3, 96.0]	0.234
During sleep	92.9 [91.2, 94.7]	91.0 [88.9, 94.8]	0.016
Minimum	85.7 [83.8, 89.2]	83.7 [81.9, 88.8]	0.071
TST90	1.8 [0.0, 10.8]	25.6 [0.5, 53.5]	0.005

Median [interquartile ranges] values are shown except for 'during sleep' (means).

measured using the Jaeger MS Masterscreen Body Box (Jaeger, Hoechberg, Germany).

Both the closed circuit multi-breath helium dilution and body plethysmography techniques permit the assessment of lung hyperinflation. However, the helium dilution method can only measure the volume of gas in the lungs in direct communication with the airways, whereas the body plethysmography technique is not affected by the presence of poorly ventilated air sacs. The difference in FRC obtained during the procedures is therefore used to calculate the trapped gas volume.

Statistical Analysis

The primary endpoints were the mean nocturnal SaO₂ and the percentage of TST90 for the comparison of salmeterol and placebo. The expected difference in these variables, which might be clinically important, and the pooled standard deviation were specified on the basis of previously published studies on pharmacological intervention on nocturnal SaO₂ on COPD [11, 12, 23]. The required sample size to detect a difference of 2% in the SaO₂ and 10% in TST90 with 90% power at the 5% significance level was 11 subjects.

Subject baseline characteristics and measured variables are expressed as medians (interquartile ranges) and compared using the Wilcoxon signed-rank test for paired samples. $p < 0.05$ was considered statistically significant.

Results

Subject Characteristics

Consecutive patients with COPD (n = 339) attending our outpatient respiratory clinics were screened for the study; 51 patients met the inclusion criteria and were eligible for enrolment. Fifteen of these patients agreed to participate and proceeded to randomization, and 12 patients completed the study. Two subjects were withdrawn as they experienced an infective exacerbation of COPD during the study period, 1 subject after 2 weeks while on salmeterol and a further subject after 5 weeks currently

Table 3. Effect of salmeterol versus placebo on duration of sleep stages, latency to persistent sleep and latency to REM sleep (n = 12)

Parameter	Salmeterol	Placebo	p value
Total sleep time, h	5.1 [4.2, 6.0]	5.1 [4.5, 6.0]	0.473
Sleep maintenance efficiency, %	81.5 [69.1, 87.8]	77.2 [66.4, 80.5]	0.875
Stage 2, %	59.3 [49.2, 65.8]	52.5 [42.8, 59.4]	0.308
Stage 3/4, %	8.3 [3.8, 12.6]	13.6 [0.0, 24.0]	0.173
REM, %	16.6 [9.7, 20.4]	17.8 [5.5, 21.9]	0.844
Total sleep time spent supine, %	30 [5, 72]	39 [5, 52]	0.359
Latency to persistent sleep, min	25.3 [15.1, 34.3]	29.0 [12.5, 38.3]	0.814
Latency to REM sleep, min	101.8 [14.0, 230.0]	127.0 [69.1, 260.0]	0.424
Arousal index, n/h	18.2 [9.0, 27.3]	18.9 [8.5, 25.4]	0.844
Apnea/hypopnea index	1.5 [0.1, 5.7]	0.2 [0.0, 2.2]	0.065

Values represent medians [interquartile ranges].

on placebo. One subject withdrew after the 2nd sleep study night. Baseline characteristics of the entire study population and, separately, the 12 subjects completing the study protocol are given in table 1.

Oxygen Saturation

The principal comparators were the SaO_2 levels during sleep between treatment with salmeterol and placebo. There was no difference in awake SaO_2 between both treatments (table 2). However, patients on placebo spent significantly more time during sleep below 90% (TST90, $p < 0.01$) and, furthermore, the mean SaO_2 during sleep was significantly lower than on salmeterol ($p < 0.02$). There was also a trend towards lower minimal SaO_2 while on placebo ($p = 0.07$; table 2).

Sleep Quality

PSG data are presented in table 3. In general, there was a wide variation in sleep quality between subjects, however there was no significant difference between studies on salmeterol and placebo. Furthermore, there were no significant differences in subjective daytime sleepiness and placebo, as assessed by the ESS. The ESS in the salmeterol arm was 3.5 [2.0, 5.0] versus 4.0 [2.0, 5.75] in the placebo arm, both values being within the normal range. In addition, there was no difference in quality of life as assessed by the SF-36 questionnaire between salmeterol and placebo.

Pulmonary Function Testing

Salmeterol had no significant effect on spirometry and diffusing capacity in our cohort (table 4). Lung volumes measured by body plethysmography and helium dilution showed a trend towards a fall with salmeterol. This was

Table 4. Effect of salmeterol versus placebo on pulmonary function testing (n = 12)

Parameter	Salmeterol	Placebo	p value
FEV ₁ , liters	0.95 [0.65, 1.06]	0.86 [0.70, 0.98]	0.140
FVC, liters	1.80 [1.67, 2.53]	1.87 [1.65, 2.33]	0.423
FEV ₁ /FVC, %	40.3 [33.7, 51.9]	39.9 [34.3, 52.0]	0.724
DLCO, % of predicted	55.0 [32.3, 63.8]	43.5 [34.4, 63.8]	0.766
Box TLC, liters	7.74 [5.95, 8.96]	8.71 [5.71, 9.22]	0.583
Box RV, liters	5.03 [3.64, 5.79]	5.46 [3.38, 6.95]	0.117
Box FRC, liters	5.73 [4.15, 6.75]	6.38 [4.03, 7.26]	0.099
He FRC, liters	4.17 [3.08, 4.83]	3.93 [3.16, 4.89]	0.158
Trapped gas volume, liters	1.19 [0.63, 1.49]	1.52 [1.01, 2.81]	0.071

Values represent medians [interquartile ranges]. FVC = Forced vital capacity; DLCO = carbon monoxide diffusing capacity; He = helium; TLC = total lung capacity; RV = residual volume; trapped gas volume = box FRC – helium FRC.

particularly evident in the trapped gas volume ($p = 0.07$), which represents the difference between FRC measured by body plethysmography and helium dilution.

Discussion

The present findings indicate that addition of the inhaled LABA salmeterol improves SaO_2 during sleep in patients with advanced COPD. Based on the PFT results we propose a reduction in hyperinflation as one likely underlying mechanism in this improvement. The magni-

tude of improvement in sleep-related SaO_2 as measured by the mean sleep SaO_2 is comparable to that previously reported with theophylline [11] and tiotropium [12] therapy. We also measured TST90, which is probably a clinically more relevant variable. Our findings demonstrate a large improvement from about a quarter of TST90 while on placebo to only 2% of sleep on salmeterol, an extent which, given the relatively small study population and the study period, is impressive and clinically relevant, as nocturnal desaturation in COPD has been reported to predispose to cardiac arrhythmias [5], elevated pulmonary arterial pressure levels during sleep [7] and nocturnal death during exacerbations [6].

The principal mechanisms of hypoxemia during sleep in COPD are a fall in minute ventilation and worsening of preexisting ventilation-perfusion mismatching. Furthermore, loss of accessory muscle activity during REM sleep may contribute to hypoventilation and thereby to a deterioration in pulmonary gas exchange [4]. There is a close relationship between the awake arterial oxygen tension and nocturnal SaO_2 levels [24]; however, even patients with mild hypoxemia have been reported to develop significant nocturnal desaturation, which may predispose to pulmonary hypertension [25]. Other studies support an improvement in lung function as an important mechanism of improvements in SaO_2 during sleep. Oral theophylline therapy reduces the degree of air trapping in the lungs with consequent improvements in sleep SaO_2 [11]. Another multicenter study performed in the United Kingdom and Ireland assessed the effect of the long-acting anticholinergic agent tiotropium and reported a similar significant improvement in SaO_2 during sleep, which was accompanied by an improvement in spirometry [12]. Furthermore, Postma et al. [23] found that the nocturnal fall in SaO_2 occurring in COPD patients was abolished by the β -agonist terbutaline in a slow-release oral form, which was also associated with an improvement in FEV_1 . β -Agonists in this form are now rarely used and the present study is the first to study the effect of an inhaled LABA, which is widely used in moderate/severe COPD, on SaO_2 levels during sleep. Although there was a trend to improved pulmonary function in our study population while on salmeterol, particularly in static lung volumes and in trapped gas volume, our study was not sufficiently powered to detect a statistically significant difference. However, previous studies comparing salmeterol and placebo reported a significant improvement in static lung volumes with salmeterol [15–17, 26] leading to improved exercise capacity and a reduction in dyspnea perception. It is likely,

given the magnitude of improvement in SaO_2 during sleep, that reduction in hyperinflation is not the only underlying mechanism of salmeterol in this process and further targeted studies need to be undertaken to specifically address this point.

The present study findings are consistent with previous reports that have failed to show a relationship between correction of hypoxemia and sleep quality in COPD [8, 12, 27]. Sleep quality is generally poor in patients with COPD and PSG studies demonstrate sleep fragmentation with frequent arousals and diminished slow wave and REM sleep [27]. This is particularly evident in hypoxemic patients and those with severe airflow limitation [9]. In our study, all patients achieved at least 4 h of objectively confirmed sleep assuring good quality studies. However, patients reported frequent awakenings in keeping with previous observations [28]. Salmeterol did not improve variables of sleep quality, but a beneficial effect may require more prolonged treatment or a larger sample size given the high degree of variability in sleep quality in this patient population. While there appeared to be a trend towards less slow-wave sleep with salmeterol, our study was not sufficiently powered to detect a significant difference and further studies would be required to specifically address this point. Notably, there was no deterioration in subjective sleep quality with salmeterol in our patient population as previously reported in another study [29]. Similar to other reports [12, 30], patients in our study did not complain of daytime sleepiness, suggesting that their sleep was not disrupted sufficiently to be perceived as non-restorative, or alternatively, their overall disease perception placed the sleep disturbances into the background.

We excluded patients with obstructive sleep apnea syndrome (OSAS) from the study to avoid a potentially important confounding disorder that might have compromised the ability to assess the direct effects of salmeterol on oxygen levels in COPD patients while asleep. Nonetheless, we recognize the importance of coexisting COPD and OSAS (commonly referred to as the 'overlap syndrome'), which is likely to be common given the high prevalence of each disorder. The degree of oxygen desaturation during sleep is greater in the overlap syndrome than with either disorder alone [31], but we cannot assess whether salmeterol would have a greater or lesser effect on sleep SaO_2 levels in such patients. This question has important practical significance since nocturnal oxygen desaturation has been identified as the most important determinant of systemic inflammation

in OSAS patients [32] and in patients with COPD, and systemic inflammation is regarded as an important factor in the development of cardiovascular complications of each disorder [33, 34]. Thus, medication that reduces the degree of nocturnal oxygen desaturation in COPD, with or without OSAS, may have an added value in terms of reducing the potential for cardiovascular complications.

A potential limitation of our study is the reliance on subjectively reported compliance. However, the dosage counter on the Diskus device in conjunction with the diary recordings completed by each patient suggests very good compliance. The patient's technique in using the device was assessed by a respiratory specialist nurse prior

to the study and corrective advice was given where necessary. Only subjects who were able to use the Diskus adequately were included in the study.

In conclusion, the present findings provide strong evidence of a clinically significant benefit from the LABA salmeterol on sleeping SaO₂ levels in patients with advanced COPD.

Acknowledgments

We would like to thank GlaxoSmithKline, Ireland (Ltd.), for supporting the study. We are grateful to all staff members of the Sleep Laboratory at the St. Vincent's University Hospital for their help and support and all patients for participating in this study.

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