

Changes in day and night time oxygenation with protriptyline in patients with chronic obstructive lung disease

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ABSTRACT The effect of protriptyline, a tricyclic antidepressant, on sleep architecture, nocturnal arterial oxygen desaturation, pulmonary function, and diurnal arterial blood gases was investigated in an open study of 14 patients with stable chronic obstructive lung disease. Daytime and overnight measurements were made before and 2 and 10 weeks after they started protriptyline (20 mg daily at bedtime). Two patients had to be excluded before the second visit and one before the third visit because of changes in treatment for their chest disease. Protriptyline caused mouth dryness in all patients and dysuria in six men. With protriptyline there were no significant changes in total sleep time, sleep period time, or the percentages of total sleep time occupied by stage I-II and stage III-IV sleep. The mean (SEM) percentage of total sleep time spent in rapid eye movement (REM) sleep decreased from 11.1 (1.7) to 4.6 (0.7) at two weeks and to 4.2 (1.0) at 10 weeks. After protriptyline the time spent during sleep with an arterial oxygen saturation (SaO_2) below each 5% increment above 65% was less than the baseline time; the lowest SaO_2 (%) reached during sleep increased from 64.5 (1.7) to 72.7 (2.1) at 2 weeks and to 77.4 (2.1) at 10 weeks. Lung volumes and expiratory flows were unchanged during the study. Daytime arterial oxygen tension (PaO_2) increased from 57 (1.4) mm Hg before treatment to 62 (1.9) mm Hg at 2 weeks and to 66 (1.9) mm Hg at 10 weeks (7.6 (0.2), 8.3 (0.3), 8.8 (0.3) kPa). Carbon dioxide tension fell from 52 (2.3) mm Hg to 49 (1.4) mm Hg at 2 weeks and to 48 (2.0) mm Hg at 10 weeks (6.9 (0.3), 6.5 (0.2), 6.4 (0.3) kPa), but these changes were not significant. These results suggest that protriptyline may benefit patients with chronic obstructive lung disease by reducing the sleep induced falls in SaO_2 and improving diurnal PaO_2 ; a controlled trial is now required.

Introduction

Polysomnographic studies show that nocturnal arterial oxygen desaturation occurs frequently in patients with chronic obstructive lung disease,¹ and that oxygen desaturation is more pronounced during rapid eye movement (REM) sleep.² Many factors, including change in airway resistance,³ ventilation-perfusion abnormalities,⁴ and alveolar hypoventilation,⁵ may play a part in this fall in arterial oxygen saturation (SaO_2). Whatever the mechanisms, repeated drops in SaO_2 during sleep and the resulting rise in pulmonary vascular resistance⁶ may contribute to the development of pulmonary hypertension and

cor pulmonale.

Continuous oxygen therapy remains the most effective treatment of sleep induced oxygen desaturation in chronic obstructive lung disease.⁷ Because the most severe falls in SaO_2 occur during REM sleep, our hypothesis was that a reduction in time spent in this sleep stage would also limit sleep induced desaturation. As tricyclic antidepressants reduce the amount of time spent in REM sleep, we evaluated the effects of a non-sedating tricyclic drug, protriptyline, on diurnal pulmonary function, sleep architecture, and nocturnal oxygen desaturation in patients with stable chronic obstructive lung disease.

Methods

PATIENTS

We studied 14 outpatients with chronic obstructive

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lung disease and a forced expiratory volume in one second (FEV_1) less than 65% predicted, an FEV_1 /forced vital capacity (FVC) ratio of less than 65%, and an ambient air arterial oxygen tension (PaO_2) while seated of 65 mm Hg* or less. Two patients were excluded before the second visit because the treatment for their chronic obstructive lung disease had been changed. Six patients were being followed for their lung disease in our institution and six had been referred for sleep studies (four for evaluation of the need for nocturnal oxygen therapy, two because the sleep apnoea syndrome was suspected). Clinical state and treatment were unchanged for at least four weeks preceding the start of the study. No subject was receiving diurnal or nocturnal oxygen therapy.

PROTOCOL

Subjects were evaluated on three occasions: before receiving protriptyline (baseline visit) and after two and 10 weeks of protriptyline treatment. At each visit pulmonary function tests and a polysomnographic study were carried out. After the baseline visit subjects took 20 mg protriptyline (Merck Frosst) once a day at bedtime. Patients were asked to bring their unconsumed medication at each visit.

The week 2 study was not carried out in two patients because of technical problems, and one patient who developed bronchopneumonia was not evaluated at 10 weeks. We therefore present data from 12 patients (seven of them men)—10 at 2 weeks and 11 at 10 weeks.

PULMONARY FUNCTION TESTS AND SLEEP STUDIES

Lung volumes were measured by body plethysmography, and forced expiratory flows by a rolling seal spirometer (PK Morgan, Chatham).⁸ Arterial blood

was withdrawn for gas analysis with the patient seated and breathing room air. The sleep studies were done by standard polysomnographic techniques.⁹ Respiratory movements of the rib cage and abdomen were measured by respiratory inductive plethysmography (Respirace, Ambulatory Monitoring, Ardsley, New York), arterial oxygen saturation was monitored with an ear oximeter (Biox IIA) and nasal and mouth airflow were measured by thermocouples (Grass Instruments, Quincy, Massachusetts). All measurements were recorded continuously on a polygraph (Model 78 D, Grass Instruments) at a paper speed of 10 mm/s. Sleep stages were scored in 30 second periods according to standard criteria.⁹

An episode of apnoea was defined as the absence of respiratory flow for at least 10 seconds. The number of episodes per hour of sleep was the apnoea index. At the first visit a second consecutive polysomnographic study was carried out in four patients whose total sleep time was less than four hours during the first night. For each polysomnographic study we assessed the characteristics of the sleep and the cumulative SaO_2 curve during sleep. The sleep period time was defined as the time from the first to the last non-awake period, the total sleep time as the sleep period time less the time spent awake in the course of it, and sleep efficiency as the ratio total sleep time:total time in bed. The cumulative SaO_2 curve was derived from the percentage of total sleep time spent below each SaO_2 value under 90%. Since the accuracy of the Biox II A oximeter is uncertain for SaO_2 values below 60%, these were included in the category <60%.

ANALYSIS

As our data were not normally distributed, we used non-parametric multiple comparison tests to compare diurnal and nocturnal measurements at 2 and 10 weeks with the baseline values (Friedman test for differences between visits and Dunnett's procedure for non-parametric values for differences from baseline values).¹⁰

*1 mm Hg \approx 0.133 kPa.

Table 1 Individual patients' characteristics and results of pulmonary function tests at baseline visit

Patient No (Sex)	Treatment	Age (y)	Weight (% IBW)	TLC l (% predicted)*	FRC (l)	ERV (l)	FEV_1 (l)	FVC (l)	PaO_2 (mm Hg)	$Paco_2$ (mm Hg)
1 (M)	TS	62	143	7.56 (119)	4.33	0.61	1.60	2.44	57	44
2 (F)	TSP	68	139	4.46 (108)	3.19	0.25	0.97	1.45	57	47
3 (M)	TD	56	145	6.51 (123)	2.14	0.79	0.94	1.53	55	48
4 (M)	T	65	129	5.72 (94)	4.04	0.88	0.93	2.28	62	41
5 (F)	TS	58	141	5.19 (128)	3.92	0.50	0.61	1.20	57	56
6 (M)	TSP	70	135	7.11 (125)	5.83	0.88	0.93	1.88	56	69
7 (M)	TS	59	92	7.01 (121)	3.85	0.82	1.56	2.49	57	54
8 (M)	T	63	95	6.92 (100)	4.92	0.63	1.46	2.57	62	52
9 (M)	TSD	65	94	6.45 (108)	4.87	0.66	0.73	1.77	56	57
10 (F)	T	57	101	4.32 (99)	3.23	0.36	0.64	1.51	65	51
11 (F)	TSD	52	135	5.83 (122)	3.82	0.56	1.04	2.00	54	48
12 (F)	TD	55	93	5.77 (136)	4.19	0.34	0.43	1.61	46	63

*On the basis of normal values from the European Community for Coal and Steel.²¹

T—theophylline; S—inhaled sympathomimetic; P—inhaled parasympatholytic; D—diuretic; TLC—total lung capacity; FRC—functional residual capacity; ERV—expiratory reserve volume; FEV_1 —forced expiratory volume in one second; FVC—forced vital capacity. Conversion—traditional to SI units: 1 mm Hg \approx 0.133 kPa.

Table 2 Results of pulmonary function tests (mean (SEM) percentages of predicted values)

Visit	TLC	FRC	ERV	FVC	FEV ₁
Baseline (n = 12)	119.6 (6.0)	158.7 (17.5)	82.6 (14.3)	56.0 (2.9)	40.8 (3.9)
2 weeks (n = 10)	132.2 (6.6)	158.2 (19.2)	78.2 (22.2)	59.2 (2.5)	42.4 (4.6)
10 weeks (n = 11)	117.8 (5.8)	158.1 (18.3)	96.6 (15.9)	59.2 (2.7)	46.0 (3.9)

Abbreviations as in table 1.

Results

The mean (SEM) age of the 12 patients was 63 (1) years and weight (percentage of ideal body weight (120% (7.5) (table 1). Weight did not change during the study period. Each patient took protriptyline as prescribed. Dry mouth, dysuria, and constipation were the only side effects noted. No study was discontinued because of side effects, though the dose of protriptyline was reduced to 10 mg once a day after 2 weeks' treatment in two patients because of severe dryness of the mouth. The results at 10 weeks in these patients were similar to those of the other patients and have not been analysed separately. There was no significant change in lung volumes or forced expiratory flows during the study (table 2). PaO₂ increased from 57 (1.4) to 62 (1.9) mm Hg at 2 weeks (p < 0.05) and to 66 (1.9) mm Hg at 10 weeks (p < 0.01) (fig 1). The fall in carbon dioxide tension (PaCO₂) from 52 (2.3) to 49 (1.4) mm Hg at 2 weeks and to 47.9 (2.0) mm Hg at 10 weeks (fig 1) was not significant. Arterial pH and bicarbonate concen-

trations remained unchanged, being 7.38 (0.07), 7.39 (0.07), and 7.38 (0.09) and 29.6 (1.1) mmol/l, 28.2 (0.7) mmol/l, and 27.0 (0.6) mmol/l at the three visits.

Nine of the 12 patients noted a subjective improvement in sleep quality. The mean total sleep time was 5.17 (SEM 0.21) hours and the sleep period time 6.61 (0.28) hours at baseline and did not change during the study. Sleep efficiency (%) was 77.9 (3.3), 81.4 (2.7), and 83.0 (2.6) at the three visits (p > 0.05). The composition of non-REM sleep in stage I-II and stage III-IV was not modified with protriptyline (fig 2). The percentage of the total sleep time spent in REM sleep decreased from 11.1 (1.7)% at the baseline visit to 4.6 (0.7) and 4.2 (1.0) (both p < 0.05) (fig 2).

The mean apnoea index was less than 5 in all patients for all visits. Sleep induced oxygen desaturation occurred in every subject, the largest fall in SaO₂ occurring during REM sleep. Values for patient 12 were excluded from the analysis as the lowest baseline SaO₂ value was undetermined (< 60%) and the week 10 visit was missed because of bronchopneumonia.

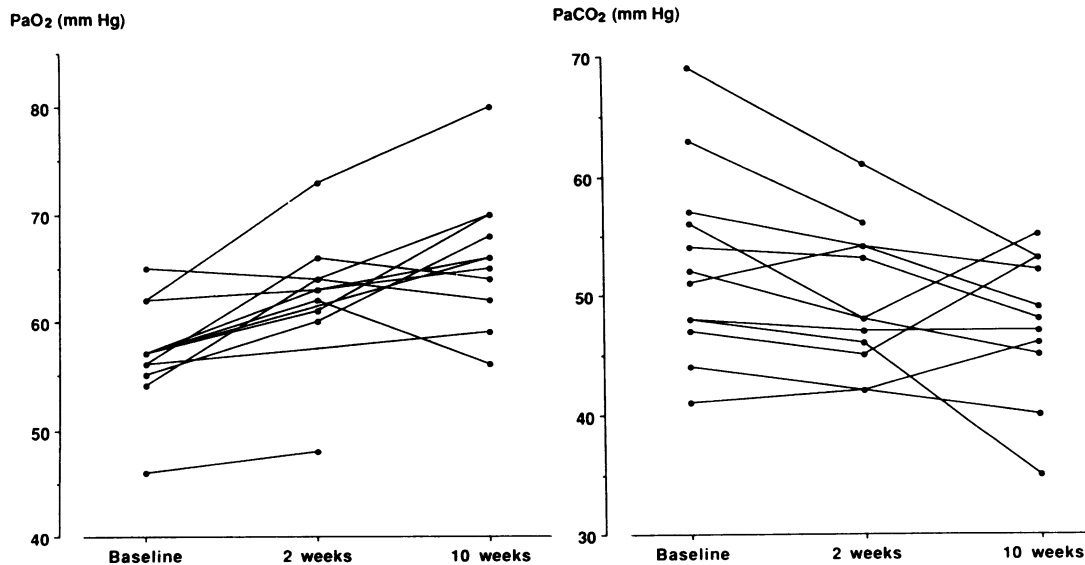


Fig 1 Individual arterial oxygen and carbon dioxide tensions (PaO₂ and PaCO₂) at each visit: before treatment (baseline) and after two and 10 weeks of protriptyline. Changes in PaCO₂ were not significant whereas PaO₂ increased significantly after two and 10 weeks (p < 0.05).

% Total sleep time

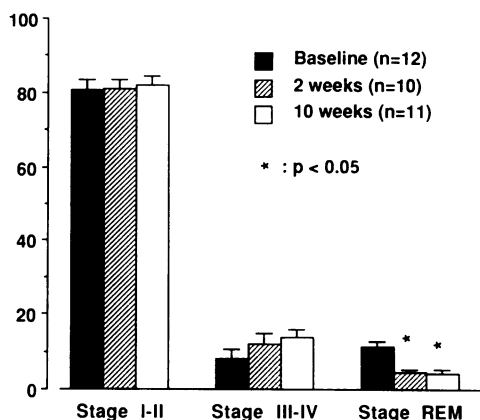


Fig 2 Sleep architecture for all subjects at each visit (means with SEM). REM sleep significantly decreased with protriptyline while the composition in stage I-II and stage III-IV sleep remained unchanged.

For the other subjects the lowest REM sleep SaO_2 (%) increased from 64.5 (1.7) to 72.7 (2.1) at 2 weeks ($p < 0.05$) and to 77.4 (2.1) at 10 weeks ($p < 0.01$).

When the patients were taking protriptyline the cumulative SaO_2 curves (percentage of total sleep time spent below each SaO_2 value) were shifted downwards

% Total sleep time

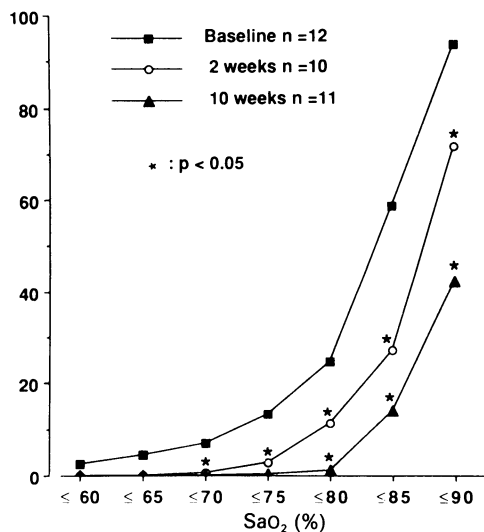


Fig 3 Cumulative distribution of mean total sleep time spent below given oxygen saturation (SaO_2) levels for all subjects. The decrease in time spent under a given saturation was significant for values greater than 65%.

and to the right (fig 3). Less time was spent with SaO_2 below each saturation value at 2 and 10 weeks than at baseline for both REM and non-REM sleep; these decreases were significant for all 5% increments in SaO_2 greater than 65%. Similar results were obtained when analysis was restricted to the nine patients who were studied at all three visits.

Discussion

Our findings indicate that protriptyline reduces the sleep induced fall in SaO_2 and increases daytime Pao_2 . Most of our patients noted an improvement in sleep quality. This improvement could be related to the increase in the amount of time spent in slow wave sleep. Nocturnal oxygen therapy has also been reported to increase the percentage of stage III-IV sleep, although this increase was not significant.¹¹

As our protocol had no blind placebo arm, we have to consider whether the changes we observed could be related to spontaneous variations in Pao_2 and sleep architecture. Although one inclusion criterion was a period of clinical stability for at least four weeks without any change in treatment for chronic obstructive lung disease, spontaneous improvement with time cannot be totally ruled out. We believe that it could not account for our findings for four reasons. (1) Four patients had pulmonary function tests, arterial blood gas measurements, and polysomnographic studies before the initial baseline visit (12 months before for patient 5, two months for patients 1 and 6, and two weeks before for patient 11). They were clinically stable throughout this period and none of the measurements we made had changed before they started protriptyline (the prestudy and the initial baseline Pao_2 values were as follows: 58 and 57 mm Hg for patient 1, 61 and 57 mm Hg for patient 5, 57 and 54 mm Hg for patient 11, and 56 mm Hg at each visit for patient 6). (2) The Pao_2 , the percentage of the total sleep time spent in REM sleep, and the depth of REM induced oxygen desaturation were modified in the same direction in all patients. (3) We observed a dramatic improvement in Pao_2 whereas the decrease in $Paco_2$ was not significant and expiratory flow rates were unchanged. If our results had been related to an improvement in their chronic obstructive lung disease, any increase in Pao_2 should have been accompanied by an improvement in $Paco_2$ and expiratory flow rates. (4) Our findings are consistent with those of previous reports of protriptyline treatment in the sleep apnoea syndrome^{12,13} and in patients with restrictive chest wall disease,¹⁴ where nocturnal oxygen desaturation and diurnal hypoxaemia improve with protriptyline.

As none of our patients had restrictive disease or an apnoea index greater than 5 and their sleep characteristics were similar to those usually encountered in patients with chronic obstructive lung disease,¹⁵ the effect of protriptyline on nocturnal SaO_2 and diurnal

Pao₂ may be attributed to the effect of this drug in chronic obstructive lung disease. We can only speculate about the mechanisms by which protriptyline improved oxygenation in these patients. The decrease in the percentage of total sleep time spent with low Sao₂ values may be related to the decrease in REM sleep that occurred with protriptyline. Besides causing a quantitative reduction in REM sleep, protriptyline may affect the mechanisms underlying oxygen desaturation during REM sleep in chronic obstructive lung disease—by, for example, improving the chemoresponse to hypoxia and hypercapnia¹⁶ or increasing the tone of the upper airway dilators¹⁷ or skeletal respiratory muscles.¹⁸

It is not clear how the effects of protriptyline on REM induced desaturation would improve oxygen saturation during non-REM sleep and during the day: preventing falls in Sao₂ by supplemental oxygen therapy does not improve diurnal Pao₂.¹⁹ These diurnal and nocturnal changes in arterial oxygenation could both be explained by a 24 hour effect of protriptyline, the main effect being an increase in daytime Pao₂, with consequent improvement in oxygen saturation throughout the night. The plasma half life of protriptyline varies from 54 to 198 hours,²⁰ so the drug may be active over the 24 hours with once daily administration.

Paco₂ did not decrease significantly with protriptyline; similar results (improvement in nocturnal Sao₂ and daytime Pao₂ without a significant change in Paco₂) have been reported with protriptyline in patients with restrictive chest wall problems.¹⁴ These results suggest that the changes in day and night time oxygenation are not related to an increase in alveolar ventilation only. Another possible explanation is an improvement in ventilation-perfusion matching by enhancement of the hypoxic pulmonary vasoconstriction in poorly ventilated lung units and thus a decrease in venous admixture.

Whatever the exact mechanisms of the improvements of diurnal and nocturnal hypoxaemia, our data suggest that protriptyline may have important effects in preventing or at least delaying the onset of chronic hypoxaemia in patients with chronic obstructive lung disease. The results of this open study have to be confirmed by a controlled trial.

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