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A Double-Blind Trial of Protriptyline in the Treatment of Sleep Apnea Syndrome

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Eight male subjects with sleep apnea syndrome were given placebo and protriptyline in a double-blind crossover design to evaluate the effects of protriptyline on respiration during sleep. Treatment with protriptyline produced significantly better oxygenation and significantly fewer arousals during sleep, but sleep staging was unchanged. The decreased number of respiratory events approached significance and was much greater in six of eight subjects. A rapid eye movement sleep-suppression explanation of the improvement in oxygenation is not supported. Alternative explanations of these findings are discussed. (Henry Ford Hosp Med J 1988;36:5-8)

Obstructive sleep apnea is characterized by episodes of upper airway obstruction which prevent airflow during sleep. Hypersomnolence and cardiovascular changes, including precipitous decreases in blood hemoglobin oxygen saturation, elevated PCO_2, and marked cardiac arrhythmias, are associated with chronic sleep apnea syndrome. Despite these abnormalities in sleep-related respiratory function, most patients with this disorder have normal respiration during wakefulness (1).

Treatments for obstructive sleep apnea are surgery or nasal continuous positive airway pressure (CPAP). Surgical treatment consists of tracheostomy and more recently uvulopalatopharyngoplasty (UPPP). Tracheostomy, while completely effective, is subject to both medical and psychological complications. UPPP has been shown to be effective only in a selected subgroup of patients with sleep apnea syndrome (2,3). Generally, these procedures are indicated in cases of severe sleep apnea syndrome. The development of nasal CPAP as a treatment for apneic episodes is an alternative in patients with moderate to severe apnea but is not well tolerated in all patients, particularly in those with mild apnea. Other treatment options, particularly for those patients with mild to moderate apnea, are needed.

Protriptyline is a tricyclic antidepressant which has a side effect profile similar to other tricyclic drugs, except that protriptyline is nonsedating. Several studies have suggested that treatment with protriptyline may improve obstructive apnea (4-7). The reported degree of success varies in these studies, as does the experimental methodology employed. Two uncontrolled studies reported sustained improvements in frequency and duration of apneic episodes in 57% (8/14) and 44% (4/9) of the patients treated with protriptyline (4,5). Daytime hypersomnolence was also reported to improve. In both studies, the patients with less severe apnea (as determined by number of events) were more likely to respond than those with severe apnea.

The only controlled study (6) used a double-blind crossover design (placebo/drug) to assess treatment in five male subjects with moderate apnea. These authors reported significant improvement in measures of oxygenation which were attributed to the rapid eye movement (REM) sleep-suppressing effect of protriptyline. Obstructive apneas in REM sleep are longer and have greater oxygen desaturation than non-REM sleep apneas, and thus overall oxygenation values improve when the number of REM events decreases significantly, even though no change occurs in the total number of events. Another study (7) also suggests that decreased REM sleep is the mechanism which leads to better oxygenation during the night in patients with apnea. Further, during non-REM sleep, many apneic episodes became hypopneic episodes which also contributed to less hypoxemia in these patients.

The present study was undertaken to study under controlled conditions the effects of treatment with protriptyline in a population of patients having mild to moderate apnea.

Methods

The study included eight male subjects, aged 31 to 54 (mean 44.9 ± 7.8 years), with obstructive sleep apnea. These subjects were selected if they complained of daytime sleepiness and had an apnea index of at least 10. The average sleep onset latency across naps from the Multiple Sleep Latency Test (MSLT) was 5.3 ± 2.5 minutes. All subjects were obese with ideal body weight ranging from 124% to 187%. Six subjects had essential hypertension, and three were diagnosed as having chronic obstructive pulmonary disease. Two subjects had more serious

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Table 1
Means and Standard Deviations of Sleep Parameters

	TST (min)	SE	%1	%2	%REM	LAT2 (min)	LAT REM (min)	WDS (min)	AAR/ HR-TST
Placebo									
Mean	403.3	83.0	54.2	33.8	10.3	20.0*	85.6*	75.8	72.6†
SD	72.4	12.4	20.2	15.4	7.2	38.3	43.1	56.8	13.9
Protriptyline									
Mean	424.6	86.7	57.8	34.2	6.9	26.8	164.5	60.6	40.7
SD	42.7	8.3	18.1	15.5	5.2	39.7	76.1	42.6	13.6

*$P < 0.05$
†$P < 0.01$
TST = total sleep time, SE = sleep efficiency, %1 = percent stage 1, %2 = percent stage 2, %REM = percent stage rapid eye movement, LAT2 = latency to stage 2, LAT REM = latency to stage REM, WDS = wake during sleep, and AAR/HR-TST = arousal associated with respiration per hour of TST.

problems: one had chronic renal failure and received treatment with dialysis three times each week, and another had a history of congestive heart failure. Medications aside from the study drug were used by five subjects and consisted primarily of diuretics. Bronchodilators were used by two subjects and antihypertensive drugs by two others.

The initial evaluation included a physical examination, a sleep history, clinical polysomnography (CPSG), and a MSLT. Polysomnograms consisted of five channels with standard placements for continuous monitoring of the central (C3) and occipital (OZ) EEGs, the horizontal electrooculogram, and the submental electromyogram (8). A V5 ECG lead was used to monitor heart rate. An additional four channels of respiratory recordings included nasal and oral airflow, diaphragmatic respiratory effort, and blood oxygen saturation measured by a Hewlett-Packard ear oximeter. Sleep stages were scored according to standard criteria (8).

A double-blind placebo-controlled crossover design with two treatment conditions was used. Subjects were randomly assigned to one of the two sequences (placebo first or drug first). Identical 10 mg capsules of placebo or protriptyline were administered for three weeks. After ten days of each drug treatment, each subject was interviewed to assess compliance with the protocol and the subjective degree of response. If no subjective improvement in symptoms was observed, the dosage was increased to 20 mg. Half the subjects received increased dosages of protriptyline, and 75% received increased dosages of placebo. After three weeks of nightly administration, the outcome evaluation which included a nocturnal CPSG and subjective ratings of daytime sleepiness was performed. Arterial blood gases were obtained and ventilatory response to hypercapnia was measured the following day. Protriptyline blood levels were tested at the end of each three-week trial to assess compliance with the respective drug regimens. The second drug trial was initiated immediately following completion of the first trial. The entire protocol was completed in six weeks for each subject.

Results

Analysis

Mean values from each group for each parameter were compared with matched groups *t* tests. Criterion for significance was set at $P = 0.05$.

Sleep parameters

Most sleep parameters were nearly identical on both drug and placebo (Table 1). The REM-suppression effect of protriptyline was evident as REM latency increased significantly ($t = 2.69$, $P < 0.05$). Stage REM as a percentage of total sleep time decreased from 10.3 to 6.9. Latency to stage 2 sleep was significantly longer ($t = 2.69$; $P < 0.05$) with protriptyline as compared to placebo. Sleep fragmentation, measured by the number of arousals associated with respiration per hour of sleep, showed a significant improvement ($t = 3.77$, $P < 0.01$) from a mean of 72.6 to 40.7 with administration of protriptyline. This improvement was not reflected in percentage stage 1 sleep, which remained unchanged for the group as a whole.

Respiratory parameters

Oxygenation during sleep was significantly improved as measured by the number of minutes below 85% saturation ($t = 2.72$, $P < 0.05$) (Table 2). Frequency of apneic episodes decreased from 44.4 events per hour of sleep with placebo to 36.7 events with protriptyline, but this difference was not significant. The number of apneic episodes in REM or in non-REM sleep did not change significantly. Six subjects had a lower apnea index (mean reduction = 33%), while the remaining two worsened. Respiratory events (apneic and hypopneic episodes combined) per hour of sleep decreased from 87.3 to 65.7, which approached significance ($t = 2.22$, $P < 0.06$). All subjects had fewer respiratory events in the protriptyline condition with a mean reduction of 22% (range 2.5% to 71%).

Pulmonary functions

Waking blood gases revealed that arterial oxygen increased from 75 to 80 mm Hg with drug administration, but this change was not statistically significant (Table 3). Arterial carbon dioxide decreased in five subjects and was identical in two others. There was a trend toward reduced $PaCO_2$ with protriptyline ($t = 2.03$, $P < 0.10$).

Subjective sleepiness

Five subjects rated their daytime sleepiness as improved on protriptyline as compared to placebo. The remaining subjects

rated the two conditions equivalently, with two subjects feeling that neither treatment was helpful.

Discussion

The major finding from this study was the improvement in oxygen saturation during sleep with protriptyline administration. Subjects had significantly fewer EEG arousals associated with respiratory events. This finding is important as arousals have been shown to predict daytime sleepiness in patients with apnea (9,10). Daytime measures of sleepiness (MSLT) were not obtained, but nocturnal latency to stage 2 increased significantly, and improvement of sleepiness occurred subjectively in six subjects.

Previous studies have also reported that oxygenation improves in patients with apnea who take protriptyline. In the present study, this effect cannot be attributed to REM-suppression, as suggested by Brownell et al (6). Our subjects had low levels of REM in the placebo condition, and this did not decrease significantly during the protriptyline trial. In fact, the total REM time decreased by an average of only 11.8 minutes. The stability of several other measures also argues against REM suppression as an explanation of these data. For example, the number of apneic episodes during REM sleep, the average duration of apneic episodes, or the duration of the longest apneic episode should be significantly decreased if fewer apneic episodes during REM sleep were responsible for the improved oxygenation.

A possible mechanism through which protriptyline improves oxygen saturation was suggested by a recent study on upper airway respiratory motor activity (11). Those authors found that protriptyline enhanced respiratory activity of the hypoglossal and recurrent laryngeal nerves. Since the hypoglossal nerve innervates the genioglossal muscle, protriptyline acts to maintain the patency of the oropharyngeal airway. Increased muscle tone of the airway, particularly in the oropharynx, might lead to a reduction in the degree of obstruction and subsequently in the number of obstructive events. Smith et al (7) reported that apneic episodes are more likely to become periods of hypopnea with use of protriptyline. Alternatively, increased airway muscle tone may lead to a reduced number of severe oxygen desaturations in the presence of obstructive apnea by delaying the obstruction until later in the inspiratory phase. Consequently, greater residual volume in the lung would cause less rapid desaturation during an apneic episode. This same phenomenon has been offered as a hypothesis to explain why many patients in whom UPPP fails have markedly improved oxygenation even though their apnea index is unchanged. Surgically widening the airway and increasing airway muscle tone may be similar in this regard.

Another possibility is that protriptyline may act as a respiratory stimulant. Smith et al (7) found a significant increase in waking PaO_2 with protriptyline administration. Our study showed a statistical trend toward reduced waking $PaCO_2$ with protriptyline. Further study of this hypothesis with a larger sample size is needed.

While protriptyline does improve apnea, its effects are inconsistent. Based on the present study and prior research, some subjects show marked improvement while others are unchanged. The task of future research is to predict which patients

Table 2
Means and Standard Deviations of Respiratory and Oximetry Measures

	Placebo*	Protriptyline*
Apnea index	44.4	36.7
	(24.3)	(29.2)
Hypopnea index	42.9	29.0
	(30.4)	(16.5)
Episodes < 85% (index)	52.1†	28.4
	(15.9)	(14.1)
Minutes < 85% (index)	15.5‡	8.2
	(12.3)	(9.9)
Low oxygen (oximetry)	37.5	50.3
	(22.7)	(19.9)
Number of apneas		
REM sleep	37.3	21.9
	(26.4)	(31.8)
Non-REM sleep	255.6	235.1
	(154.9)	(204.6)
Mean duration	22.0	22.2
(seconds)	(4.4)	(5.6)
Longest apnea	61.1	57.0
(seconds)	(21.6)	(21.0)

*Means are the first reported data, standard deviations are in parentheses.
†$P < 0.05$
‡$P < 0.02$
Note: Index values are per hour of total sleep time.

Table 3
Individual Values from Pulmonary Function Tests

	PaO_2		$PaCo_2$		Ve/Co_2	
Subject	Placebo	Protriptyline	Placebo	Protriptyline	Placebo	Protriptyline
1	62	—	45	—	—	—
2	73	79	47	41	2.41	3.02
3	78	74	35	35	2.79	2.13
4	71	—	38	—	1.53	2.15
5	62	84	45	31	—	—
6	84	89	40	34	3.12	3.55
7	76	78	42	41	4.4	4.7
8	77	78	39	39	3.45	3.18
Mean	75	80.3	41.3	36.8	2.95	3.12
SD	7.3	5.3	4.3	4.1	0.97	0.96

will benefit from protriptyline therapy in the management of their sleep apnea syndrome. Also, research of other medications which may increase upper airway muscle tone and/or act as respiratory stimulants may lead to effective, safe compounds for use in the obstructive sleep apnea syndrome.

References

1. Guilleminault C, Tilkian A, Dement WC. The sleep apnea syndromes. Annu Rev Med 1976;27:465-84.
2. Fujita S, Conway WA, Sicklesteel JM, et al. Evaluation of the effectiveness of uvulopalatopharyngoplasty. Laryngoscope 1985;95:70-4.
3. Sher AE, Thorpy MJ, Shprintzen RJ, Spielman AJ, Burack B, McGregor PA. Predictive value of Muller maneuver in selection of patients for uvulopalatopharyngoplasty. Laryngoscope 1985;95:1483-7.
4. Clark RW, Schmidt HS, Schaal SF, Boudoulas H, Schuller DE. Sleep apnea: Treatment with protriptyline. Neurology 1979;29:1287-92.
5. Conway WA, Zorick F, Piccione P, Roth T. Protriptyline in the treatment of sleep apnoea. Thorax 1982;37:49-53.
6. Brownell LG, West P, Sweatman P, Acres JC, Kryger MH. Protriptyline in obstructive sleep apnea: A double-blind trial. N Engl J Med 1982;307:1037-42.
7. Smith PL, Haponik EF, Allen RP, Bleecker ER. The effects of protriptyline in sleep-disordered breathing. Am Rev Respir Dis 1983;127:8-13.
8. Rechtshaffen A, Kales A (eds). A manual of standardized terminology, techniques, and scoring system for sleep stages of human subjects. Bethesda: United States National Institute of Neurological Diseases and Blindness, 1968.
9. Roth T, Hartse KM, Zorick FJ, Conway WA. Multiple naps and the evaluation of daytime sleepiness in patients with upper airway sleep apnea. Sleep 1980;3:425-39.
10. Stepanski E, Lamphere J, Badia P, Zorick F, Roth T. Sleep fragmentation and daytime sleepiness. Sleep 1984;7:18-26.
11. Bonora M, St John WM, Bledsoe TA. Differential elevation by protriptyline and depression by diazepam of upper airway respiratory motor activity. Am Rev Respir Dis 1985;131:41-5.