

# Effects of protriptyline on sleep related disturbances of breathing in restrictive chest wall disease

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**ABSTRACT** The effects of protriptyline on sleep stage distribution and gas exchange have been assessed in eight patients with nocturnal hypoventilation secondary to restrictive chest wall disease. At a dose of 10–20 mg taken when they retired the total sleeping time was unaltered but the proportion of rapid eye movement (REM) sleep fell from 22% to 12% ( $p < 0.05$ ). The total time spent at an arterial oxygen saturation of less than 80% decreased ( $p < 0.01$ ) and the magnitude of the fall correlated with the reduction in REM sleep ( $r = 0.67$ ,  $p < 0.05$ ). There was also a reduction in the maximum carbon dioxide tension reached during the night ( $p < 0.01$ ). The arterial oxygen tension measured diurnally increased ( $p < 0.05$ ) from a median of 8.0 kPa (60 mm Hg) to 9.0 kPa (67.5 mm Hg), but the carbon dioxide tension and base excess were unchanged. Anticholinergic side effects were experienced by most patients but did not limit treatment.

Disturbances of breathing during sleep cause reduction in arterial oxygen saturation and carbon dioxide retention, which may contribute to the development of cardiorespiratory failure in patients with chronic obstructive lung disease,<sup>1</sup> restrictive chest wall defects,<sup>2–4</sup> and respiratory muscle weakness.<sup>5</sup> Episodes of hypoventilation are more common than periods of apnoea and occur predominantly during rapid eye movement (REM) sleep.

The tricyclic antidepressant protriptyline is effective in the treatment of mild to moderately severe obstructive sleep apnoea and here too the most profound episodes of desaturation occur during REM sleep. The beneficial effect of protriptyline has been attributed to a reduction in the time spent in REM sleep,<sup>6,7</sup> although there may be an additional action on upper airway tone.<sup>8</sup> The present study was undertaken to investigate the effects of protriptyline on sleep related disturbances of breathing in patients with restrictive chest wall defects.

## Methods

Treatment with protriptyline was offered to eight patients (seven of them women) with restrictive chest wall defects and documented nocturnal hypoventilation who presented in respiratory or cardio-

respiratory failure. Five had required one or more periods of mechanical support with negative pressure ventilation to control cardiorespiratory failure resistant to conventional treatment, and one had continued to use a cuirass at home until the trial began. The patients were aged from 26 to 68 (median 45) years; four suffered from idiopathic scoliosis (Cobb angle 45–84°), one had fixed rib anomalies associated with myelodysplasia, and the remaining three had restrictive defects secondary to pulmonary tuberculosis and its treatment (pleural calcification following artificial pneumothorax, thoracoplasty, phrenic crush, or avulsion). Values for vital capacity, maximum static inspiratory and expiratory mouth pressures, and arterial blood gas tensions before treatment are given in table 1. The predicted figures for vital capacity were based on the data of Cotes,<sup>9</sup> using span rather than height in the scoliotic subjects.

Polysomnography was carried out on two successive nights, the patient being acclimatised to the laboratory and its equipment during the first night and data being recorded during the second. The electrocardiogram, electroencephalogram (EEG), and electro-oculogram (EOG) were recorded from surface electrodes. Oxygen saturation (Sao<sub>2</sub>) and transcutaneous carbon dioxide tension (tcPCO<sub>2</sub>) were measured continuously with a Hewlett-Packard ear oximeter (model 47201A) and capnometer (model 47201A). Gas flow was recorded at the mouth and one nostril with thermistors mounted in light weight plastic tubing, and thoracoabdominal movement was

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Table 1 Vital capacity, maximum static inspiratory and expiratory mouth pressures, and arterial blood gas tensions before and during protriptyline treatment in eight patients

	Before treatment		During treatment		p*
	Median	Range	Median	Range	
Vital capacity (% pred)	30	21–43	30	19–42	NS
P <sub>imax</sub> (cm H <sub>2</sub> O)	38	25–60	41	30–70	NS
P <sub>emax</sub> (cm H <sub>2</sub> O)	65	39–100	62	35–70	NS
P <sub>aO<sub>2</sub></sub> (kPa)	8.0	6.2–9.9	9.0	6.8–9.8	<0.05
P <sub>aCO<sub>2</sub></sub> (kPa)	6.5	5.5–7.9	6.4	4.8–7.7	NS

\*Wilcoxon matched pairs signed rank test.

P<sub>imax</sub>—maximum static inspiratory pressure; P<sub>emax</sub>—maximum static expiratory pressure; P<sub>aO<sub>2</sub></sub>—arterial oxygen tension; P<sub>aCO<sub>2</sub></sub>—arterial carbon dioxide tension.

Conversions: SI to traditional units—Blood gas tensions: 1 kPa = 7.5 mm Hg.

detected with two pairs of magnetometers positioned anteroposteriorly. An eight channel recorder (Siemens Mingograph) was used to collect the data and a Linseis potentiometric pen recorder was also coupled to the oximeter and capnometer to facilitate subsequent digitisation.

Standard EEG and EOG criteria were used to identify sleep stages<sup>10</sup> and the total duration of wakefulness, non-rapid eye movement (non-REM) sleep, and rapid eye movement sleep was calculated, stage 1 sleep being included in total non-REM time. Arousal was considered to have occurred if the EEG showed an increase in alpha waves with a burst of activity in any other channel consistent with an electro-myographic discharge.

The continuous records of S<sub>aO<sub>2</sub></sub> and t<sub>c</sub>P<sub>CO<sub>2</sub></sub> were digitised with a Prime computer and the information was expressed graphically. The time spent within each 5% band of oxygen saturation from zero to 100% was calculated without applying any correction for values recorded at 65% or less, where the oximeter is known to under-read.<sup>11</sup> Episodes of hypopnoea were identified if there was reduction in thoracoabdominal movement of at least 50% lasting for more than 10 seconds<sup>12</sup> accompanied by continued oronasal airflow.

Polysomnography was repeated four to six weeks after treatment with protriptyline, 10–20 mg at night. The dose was chosen according to body weight and initial incidence of anticholinergic side effects and was taken at the patient's usual bedtime. Plasma protriptyline concentration was measured in six patients at the time of the second sleep study, when measurements of vital capacity, daytime arterial blood gas tensions, and mouth pressures were also repeated. No form of mechanical ventilatory assistance was used during the trial period and any other treatment was continued unchanged.

The Wilcoxon matched pairs signed rank test was used to compare total sleep time, the proportion of

REM sleep, and the time spent during sleep with an arterial oxygen saturation below 80% ( $t < 80$ ), before and during treatment with protriptyline. The same test was applied to measurements of diurnal arterial blood gas tensions, vital capacity, and static mouth pressures. The Spearman rank correlation test was used to compare the reduction in REM sleep time and  $t < 80$ .

## Results

Total sleep time was unaltered with a median of 300 (range 220–433) minutes in the initial study and 333 (range 223–415) minutes during protriptyline treatment. REM time as a percentage of total sleep time was reduced in all but one patient (fig 1). REM time for the group as a whole occupied a median of 22% of total sleep time in the initial study (range 11–25%), and fell to 12% (range 0–23%) during protriptyline treatment ( $p < 0.05$ ).

The time spent with an arterial oxygen saturation below 80% during sleep (fig 2) fell from a median of 70 (range 41–243) minutes to 22 (range 9–101) minutes. This represents a reduction from 23.5% to 7.5% of total sleep time ( $p < 0.01$ ), and there was a positive correlation between the decrease in REM sleep and  $t < 80$  ( $r = 0.67$ ,  $p < 0.05$ ).

The lowest values of oxygen saturation always occurred during REM sleep and were unaltered by protriptyline. They ranged from 14% to 58% (median 50%) before treatment and 23% to 67% (median 54%) during treatment. The highest values for transcutaneous carbon dioxide tension were also associated with REM sleep and were reduced from a median of 79 mm Hg (10.5 kPa), range 65–89 mm Hg (8.7–11.9 kPa), to 68.5 mm Hg (9.1 kPa), range 58–79 mm Hg (7.7–10.5 kPa), during protriptyline treatment. This change was significant ( $p = 0.01$ ).

The frequency and mean duration of episodes of hypoventilation were unchanged by protriptyline but

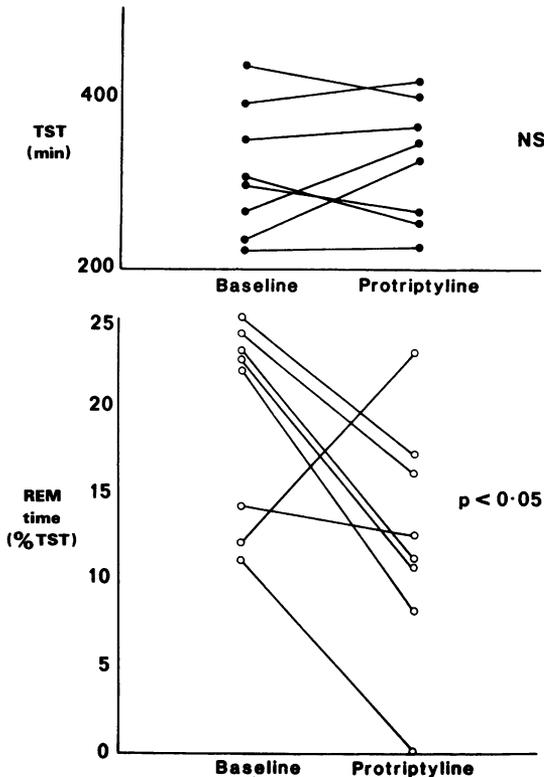


Fig 1 Top: Total sleep time (TST) before and during treatment with protriptyline. Bottom: REM time as a percentage of total sleep time before and during treatment with protriptyline.

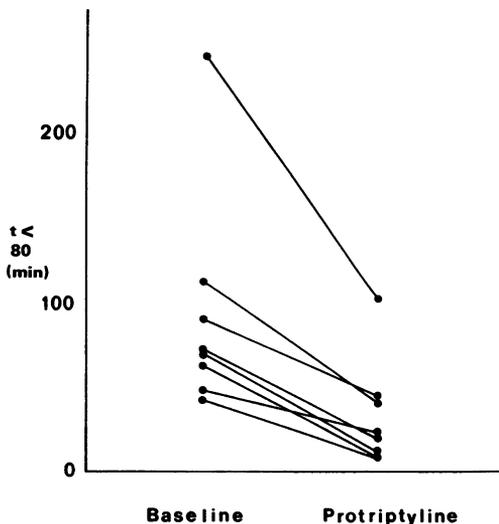


Fig 2 Time (minutes) spent with arterial oxygen saturation below 80% ( $t < 80$ ) before and during treatment with protriptyline.

the overall number of episodes was reduced because of the reduction in REM sleep. There were no episodes of central or obstructive apnoea in any patient before or during treatment.

The frequency of arousal was uninfluenced by protriptyline and there was no consistent degree of desaturation at which it occurred. Considerable variation was noted between different episodes in the same patient throughout a single night.

The resting heart rate did not change during treatment, either awake or during REM sleep, but there was a slight increase during non-REM sleep from 82 to 93 beats a minute. There was no increase in the incidence of ventricular ectopic beats and no other disturbances of rhythm were seen.

The arterial oxygen tension measured during the daytime rose significantly ( $p < 0.05$ ) from a median of 8.0 kPa (60 mm Hg), range 6.1–9.9 kPa (46–74 mm Hg), to 9.0 kPa (67.5 mm Hg), range 6.8–9.8 kPa (51–73.5 mm Hg), during protriptyline treatment. There was no change in diurnal values of arterial carbon dioxide tension or base excess, or in vital capacity or static mouth pressures (table 1).

Anticholinergic side effects were noted by most patients but regarded as tolerable. Plasma concentrations of protriptyline showed no relationship to dose (mg/kg), effect on nocturnal oxygenation, or incidence of side effects (table 2). There was no change in body weight. In a wider study of the effects of protriptyline on mixed disorders of breathing during sleep in 30 patients (15 men and 15 women), three developed hesitancy of micturition and one severe constipation; one became impotent; and one suffered postural hypotension, which might have been related to protriptyline. Treatment was withdrawn in five of these six but has been continued in the remaining 24 without any ill effect other than dryness of the mouth.

### Discussion

The patients included in this study were all severely disabled and treatment was offered in a non-blind fashion. Spontaneous improvement with time cannot

Table 2 Plasma protriptyline concentrations in six patients

Patient No	Dose (mg/kg)	Protriptyline concentration ( $\mu\text{g/l}$ )*
1	0.28	37
2	0.20	45
3	0.33	47
4	0.33	51
5	0.17	27
6	0.18	53

\*Recommended therapeutic plasma concentration for the treatment of depression 70–200  $\mu\text{g/l}$ .

be excluded but this seems unlikely because all patients had been deteriorating symptomatically at the time of referral and five had required mechanical ventilatory assistance to alleviate cardiorespiratory failure before the study began.

The findings confirm previous observations that protriptyline caused a significant reduction in the duration of REM sleep, without affecting total sleep time,<sup>6,7</sup> although this is not a universal finding.<sup>13,14</sup> Suppression of REM sleep is a property shared by other tricyclic antidepressants,<sup>15</sup> but protriptyline is unique in that it is devoid of a sedative action and thus is unlikely to accentuate nocturnal hypoventilation.

There was a reduction in the time spent with an oxygen saturation below 80%, which correlated with the reduction in REM sleep time. Episodes of nocturnal hypoventilation are known to be associated primarily with REM sleep and so a reduction in  $t < 80$  would be expected when the duration of REM sleep is curtailed. An alternative interpretation is that oxygenation at the beginning of the night was improved so that a similar fall in ventilation, and thus in arterial oxygen tension, caused a lesser fall in saturation. Daytime oxygenation and hence saturation at the start of the night were improved, and it could be argued that this represented a spontaneous change with time, rather than a consequence of treatment. There was no control period with a placebo and so this explanation cannot be ruled out entirely; but the absence of change in diurnal carbon dioxide tension, or in any other index of respiratory function, makes it unlikely.

The episodes of hypoventilation that did occur during treatment with protriptyline were unmodified in duration and severity, an observation consistent with reports of the effect of the drug in patients with obstructive sleep apnoea.<sup>6,7</sup> The reduction in the maximum value of transcutaneous carbon dioxide tension without any improvement in the worst oxygen saturation values reflects in part the technique of measurement. Transcutaneous carbon dioxide tension shows good agreement with the arterial tension in well perfused skin<sup>16,17</sup>; but despite the linear relationship, which we confirmed with the capnometer used in this study, the response time of the instrument<sup>17</sup> obliterates the detail of rapidly changing values. Thus the peak values occurring during a period of REM sleep represent the mean of a series of hypopnoeic episodes and, because treatment with protriptyline was associated with a reduction in REM sleep time and a reduction in the number of hypopnoeic episodes, the maximum value of  $t\text{PCO}_2$  was also reduced.

The findings reported here are consistent with the hypothesis that protriptyline diminished the severity

of sleep related disturbances of ventilation by reducing the duration of REM sleep. Bronchodilatation attributable to the anticholinergic properties of the drug might contribute too, but the absence of change in spirometric indices makes this unlikely. Similarly, the absence of change in maximum static mouth pressures is evidence against a direct action either on the contractility of the respiratory muscles or on ventilatory mechanics. Finally, a central respiratory stimulant effect seems unlikely because there was no change in diurnal carbon dioxide tension or base excess. Brownell *et al*<sup>6</sup> have shown that protriptyline does not influence the ventilatory response to hypercapnia in normocapnic subjects suffering from sleep apnoea, but its effects on the ventilatory response to hypoxia are unknown.

The use of protriptyline was associated in these eight patients with an improvement in nocturnal oxygenation, a reduction in the severity of nocturnal hypercapnia, and a diminution in the time spent during sleep with an oxygen saturation below 80%. There is no threshold or cumulative degree of nocturnal desaturation that is known to produce consistently harmful effects, but there is evidence suggesting that hypoxaemia during sleep contributes to the development of sustained pulmonary hypertension<sup>18</sup> and cardiac dysrhythmias.<sup>19</sup> Other regimens advocated for the treatment of nocturnal hypoventilation include oxygen treatment and almitrine for patients with chronic obstructive lung disease<sup>20-22</sup> and negative pressure ventilation for patients with restrictive defects.<sup>23,24</sup> Long term oxygen treatment prolongs survival in patients with hypoxic cor pulmonale caused by chronic obstructive lung disease,<sup>25</sup> and preliminary findings<sup>23,24</sup> suggest that negative pressure ventilation is effective in the management of patients with musculoskeletal disorders restricting ventilation. Further work will be required to confirm the benefit with protriptyline and to define its role in management.

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