The use of protriptyline for respiratory failure in patients with chronic airflow limitation

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ABSTRACT: Treatment of nocturnal hypoventilation in patients with restrictive chest wall disease and respiratory failure, results in improved daytime arterial blood gas tensions, increased functional ability and longer survival. Success has been achieved with the use of protriptyline which reduces the duration of rapid eye movement (REM) sleep during which nocturnal hypoventilation occurs. Eighteen patients with severe chronic airflow limitation (CAL), took part in a randomized, double-blind, cross-over trial of protriptyline and placebo. Seventeen patients completed the study. The use of protriptyline was associated with a fall in the median percentage of total sleep time spent in REM from 16 to 8.8% (p<0.01). This was associated with a reduction in the median daytime arterial carbon dioxide tension from 6.4 kPa (range 5.2-8.5 kPa) to 5.8 kPa (range 5.0-8.1 kPa) (p<0.01); increased respiratory muscle strength (p<0.05), and increased six minute walking distance from a median of 258 m (range 58.5-585 m) to 275 m (range 171-598 m) (p<0.02). We found pharmacological treatment of REM-related nocturnal hypoventilation in patients with CAL to be effective, but anticholinergic side-effects, particularly in older male patients, might preclude long-term treatment.

Nocturnal oxygen desaturation due to hypoventilation has been reported in patients with chronic airflow limitation (CAL), particularly during rapid eye movement sleep (REM) [1]. REM suppression by the use of protriptyline, a non-sedative tricyclic anti-depressant drug, has been shown to improve REM-related obstructive sleep apnoea (OSA) [2, 3], and REM-related nocturnal hypoventilation in patients with restrictive chest wall disease [4]. In the latter, the improvement in nocturnal oxygenation has been associated with the resolution of daytime respiratory or cardiorespiratory failure [5]. It has been suggested that the oxygen desaturation and associated transient rise in pulmonary artery pressure, seen during REM sleep in patients with CAL, may eventually lead to sustained pulmonary hypertension and cor pulmonale [6]. Although this hypothesis remains unproven, the results of REM suppression with protriptyline in other disorders characterized by nocturnal hypoventilation prompted an evaluation of its effects on nocturnal oxygenation and daytime respiratory function in patients with CAL.

Methods

Eighteen patients (13 M, 5 F) aged 33-68 yrs (median 63 yrs) with stable CAL took part in a randomized, double-blind, cross-over trial of 10 mg of protriptyline daily and a placebo. Each phase of the study was of 6 wks duration and there was no wash-out period between the two phases. All patients had severe disease (forced expiratory volume in one second (FEV1) <1200 ml, i.e. less than 40% predicted) and previously documented hypercapnia whilst in a stable state. No patient was receiving any form of sedative medication and alcohol was withheld on the days of the studies. All other existing medication was continued unaltered. Two patients were receiving long-term domiciliary oxygen therapy for 15 h per day.

Patients were admitted for 48 h for assessment on three occasions during the study. The first assessment was before commencing treatment (i.e. wk 0), the second at the end of the first phase (wk 6), and the third at the end of the second phase (wk 12). The investigations performed on each admission included polysomnography, full pulmonary function tests, maximum static mouth pressures, arterial blood gas analysis, six minute walking tests and questionnaires to assess general health, depression and breathlessness.

Each patient gave written consent to the study which was approved by the Hospital Ethical Committee.

Polysomnography

The patients were studied on two consecutive nights, the first being an acclimatization night with data recorded on the second night only. The electroencephalogram
(EEG), electro-oculogram (EOG) and electrocardiogram (ECG) were recorded throughout the night. Oxygen saturation (SaO2) was measured continuously with a Hewlett Packard ear oximeter (model 47201A), and transcutaneous carbon dioxide levels (Picco) were monitored using a Hewlett Packard capnometer (model 47201A). Gas flow was recorded at the mouth and one nostril with thermistors mounted in lightweight plastic tubing. Thoraco-abdominal movement was detected with two pairs of magnetometers positioned antero-posteriorly and secured at the level of the nipples and umbilicus. An eight channel ink recorder (Siemens Mingograf 81) was used to collect the data and a Leinseis potentiometric pen recorder was also coupled to the oximeter and capnometer to facilitate subsequent digitization.

Standard EEG and EOG criteria were used to identify sleep stages [7]. The total duration of wakefulness, total sleep time (TST) and the amounts of both non-rapid eye movement sleep (NREM) and rapid eye movement sleep (REM) were calculated. Episodes of hypopnoea were identified if there was a 50% reduction in excursion of one pair of magnetometers, associated with a 25% reduction from the other pair, lasting for more than 10 s and accompanied by continued (but reduced) oronasal airflow.

The oxygen saturation and transcutaneous carbon dioxide traces were digitized by a Prime computer and the information was expressed graphically. The percentage of TST, and the actual sleep time, spent within each decile of oxygen saturation was calculated without applying any corrections for values recorded at 65% or less.

**Pulmonary function tests and maximum static mouth pressures**

Forced expiratory volume in one second (FEV1), forced vital capacity (FVC), peak expiratory flow rate (PEFR), total lung capacity (TLC) and functional residual capacity (FRC) were measured as was the transfer coefficient (Kco). Maximum expiratory (Pmax) and maximum inspiratory (Pimmax) mouth pressures were measured using the technique of Black and Hyatt [8] and the best result from three attempts was recorded for each measurement.

**Arterial blood gas analysis**

Arterial blood was sampled from the radial artery after the instillation of local anaesthetic to the covering skin and this was then analysed immediately using a Corning blood gas analyser (model 170). Sampling was performed at the same time of day on each assessment.

**Six minute walking tests**

Two consecutive corridor walks were performed using a hospital corridor 45 m in length. On completion of the first 6 min walk, the patient was allowed a maximum of 5 min rest before beginning the second. No encouragement was given during the walk and at the end of each walk a Borg scale for perceived exertion was completed.

**Questionnaires**

a) General Health Questionnaire (GHQ 30). The GHQ is a screening device for detecting patients with minor psychiatric symptoms. The GHQ 30 is an abbreviated form with 30 questions which generates a score between 0 and 30. A score of more than 4 indicates a probable psychiatric case [9].

b) Beck Depression Inventory. This is a well-established questionnaire which provides a quantitative assessment of the intensity of depression. It is administered as a self-rating scale and contains thirteen items with 4 ranked statements to each item. A Beck score of 15 or more is considered to indicate significant depression [10].

c) Visual Analogue Scales (VAS). Nine questions (Appendix 1) were presented separately to both the patient and their spouse on each assessment. The questions referred to the degree of breathlessness experienced by the patient during moderate exertion and also to their general well being. A total score of between 0 and 90 was obtained (90 representing extreme breathlessness on all activities).

Statistical analysis was by the Wilcoxon matched pairs test unless otherwise stated, and values for p ≤ 0.05 were regarded as statistically significant.

**Results**

Seventeen patients completed both phases of this study, one male patient died during the second phase (placebo) and was excluded from analysis. Patient characteristics are given in table 1. No study was discontinued because of side-effects of the drug, although all patients noted anticholinergic effects. On direct questioning, five male patients would be reluctant to take protriptyline on a long-term basis because of urinary difficulties but in women the most troublesome side-effect was a dry mouth.

**Table 1. – Patient characteristics**

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<th>Median</th>
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</tr>
<tr>
<td>FVC ml</td>
<td>2030</td>
<td>880–3420</td>
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</table>

FEV<sub>1</sub>: forced expiratory volume in one second; % pred: percentage predicted; FVC: forced vital capacity.
Polysomnography

The median TST on entry to this study was 313 min (range 170-406 min), 298 min (range 212-442 min) during the placebo limb and 306 min (range 215-420 min) whilst taking protriptyline. The percentage of TST spent in REM sleep was 16% (range 0-24%) on entry to the study, 15% (range 9-25%) during the placebo phase, falling to 8.8% (range 1.5-16.4%) whilst taking protriptyline (p<0.01) (fig. 1).

![Graph of oxygen saturation (Sao₂) and transcutaneous carbon dioxide levels (Ptco₂) overnight in one patient. A) During the placebo phase. B) During the protriptyline phase. REM: rapid eye movement.](image)

Three patients experienced a greater amount of REM sleep during the placebo limb than during the initial assessment suggesting that further acclimatization to the sleep laboratory has taken place. Episodic accentuation of oxygen desaturation, which was REM-related, was seen throughout the night in all patients. An example of the change in oxygen saturation and Ptco₂ levels seen during the placebo and protriptyline phases of this study are given in figure 2.

The percentages of TST spent in REM sleep, on entry to the study, at the end of the placebo phase and at the end of the protriptyline phase were compared for each phase of this study. Overall oxygenation improved, but only the change in % of TST spent with an SaO₂ of <70% was statistically significant falling from 100% (range 10-100) on initial assessment and whilst taking the placebo, to 94% (range 0-100) during the protriptyline phase (p<0.05). Median values for the time spent with an SaO₂ of <80% improved from 11.5% (range 0-100%) to 2% (range 0-97%) during the protriptyline phase; and for an SaO₂ <70% improved from 2% (range 0-100%) to 0% (range 0-11%), respectively, but these changes did not achieve statistical significance.

The mean apnoea index was less than 5 in all except one patient who was found to have coincidental obstructive sleep apnoea. All other subjects had worsened oxygen desaturation during sleep as a result of hypoventilation rather than apnoea. Hypoventilation was largely continuous throughout REM periods and no attempt was made, therefore, to estimate numbers of episodes.

Pulmonary function tests and respiratory mouth pressures

No significant change in lung volumes or gas transfer occurred during either limb of this study. On initial assessment only four of the 17 patients achieved their predicted values for Pmax and Pmax [11]. Median Pmax was 100 cmH₂O (range 50-145 cmH₂O) on entry to the study: 110 cmH₂O (range 50-200 cmH₂O) during the placebo limb and 110 cmH₂O (range 60-200 cmH₂O) while taking protriptyline. Median Pmax was -40 cmH₂O on initial assessment (range -15 to -70 cmH₂O), -40 cmH₂O during the placebo limb (range -20 to -85), and -50 cmH₂O during the protriptyline phase (range -25 to -80) (p<0.01).
Arterial blood gas analysis

Patients were selected for this study on the basis of severe CAL associated with daytime hypercapnia. An elevated arterial carbon dioxide tension (Paco\(_2\)) had been recorded in all patients on two occasions during the 4 wks preceding this study, when stable by clinical criteria, but five (of seventeen) were normocapnic by day of entry to the trial. Median Paco\(_2\) on entry was 6.4 kPa (range 5.2–8.5 kPa), and during the placebo phase was 6.8 kPa (range 5.4–9.0 kPa), falling to 5.8 kPa (range 5.0–8.1 kPa) whilst taking protriptyline (p<0.01). Although the median arterial oxygen tension (Pao\(_2\)) improved from 6.9 kPa (range 4.8–10.1 kPa) on first assessment to 7.8 kPa (range 5.1–10.1 kPa) during the protriptyline phase this change did not achieve statistical significance. Median Pao\(_2\) during the placebo limb was 7.1 kPa (range 4.7–10.1 kPa) (fig. 3).

Questionnaires

Ten of the 17 patients achieved a score of more than 4 on completing the GHQ 30 (less than 4 being regarded as normal) on initial assessment. While taking placebo 8 of 17 had an abnormal score and while taking protriptyline 2 of 17 were abnormal. The median GHQ score on entry was 5 (range 0–19); 5 during the placebo phase (range 1–16), falling to 1 during the protriptyline phase (range 0–10) (p<0.01).

No patient achieved a score indicating significant depression on completing the Beck depression inventory, at any assessment. The maximum score achieved was 12 and this was in a female patient at the initial assessment. When the Beck scores for each limb of the study were completed no change of statistical significance was found.

There was no difference of statistical significance in the VAS completed by the patients, but a small increase was noted during the placebo limb when the same scale was completed independently by the spouse. The median VAS registered by the spouse was 47 (range 34–82) at entry, 54 (range 35–77) on placebo and 46 (range 12–68) on protriptyline (p<0.01).

Discussion

REM-related nocturnal hypoventilation is common in the patient with severe restrictive chest wall disease, and may contribute to the development of cardiorespiratory...
failures. Protriptyline will reduce REM sleep, improve nocturnal oxygenation, and increase the daytime arterial oxygen tension in such patients. In this study of protriptyline in patients with chronic airflow limitation, REM reduction was associated with improved nocturnal oxygenation but no significant reduction in the maximum Pco2 overnight. However, as REM time was reduced the total time spent with a carbon dioxide level above the awake value was also reduced.

The median values for daytime arterial blood gas tensions improved, although only the reduction in Pao2 reached statistical significance. It is possible that the improvement in oxygenation would have reached statistical significance if a larger number of patients had been studied. An alternative explanation is that there was an increase in ventilation/perfusion mismatch which allowed a disproportionate improvement in Pao2. Bronchodilatation resulting from the anticholinergic properties of protriptyline might, theoretically, contribute to the improvement in arterial blood gas tensions, but no change in lung function was demonstrated on formal assessment and so this is unlikely. Improved oxygenation associated with the use of protriptyline has been reported in patients with CAL [12] or restrictive lung disease [5]. The CAL study was of open design without a control arm and although the improvement in daytime arterial oxygen tension achieved statistical significance the improved carbon dioxide tension did not. As in our study less nocturnal desaturation occurred whilst the patients were taking protriptyline. Speculation about the mechanism of improvement in daytime arterial blood gas tensions includes change in central chemosensitivity, improved upper airway muscle tone and increase in respiratory muscle strength. In our study a small but statistically significant increase in Pmax was seen, but this could be due to the coincidental fall in Pao2 [13].

Functional ability and respiratory muscle strength were not assessed by Jonas et al. [12] but we found an increase in exercise capacity measured by corridor walking. The patients did not report symptomatic improvement in their breathlessness on VAS scoring and the apparent worsening of their dyspnea as judged by the spouse during the placebo limb is of questionable significance.

Chronic disease is frequently associated with depression [14], which might be relieved by the antidepressant properties of protriptyline but no patients were depressed on entry to the study as judged by the Beck Depression Inventory and, more importantly, there were no changes in the indices of depression as the study progressed. However, many patients had an abnormal GHQ score initially which was significantly reduced during the protriptyline phase, suggesting an improvement in general well-being.

An improvement in nocturnal oxygenation and daytime arterial blood gas tensions can be obtained with protriptyline and we would recommend a trial of this drug in the “blue and bloated” chronic bronchitic. Protriptyline is likely to be better tolerated in female patients as anticholinergic side-effects tend to limit treatment in older male patients in whom prostatism may be precipitated.

The provision of domiciliary oxygen can relieve nocturnal desaturation but has no effect, or an adverse effect, on the clearance of carbon dioxide. An alternative approach is to abolish hyperventilation entirely by providing mechanical assistance overnight. Currently available evidence suggests that patients with CAL fare less well than other groups, but the role of nocturnal hyperventilation in the development of cor pulmonale in CAL will remain unknown until a larger and longer trial has been undertaken of techniques which seek to abolish this sleep-related abnormality of gas exchange.

Appendix 1

Visual Analogue Scales

1. If you did any of the following this week, how breathless were you?

   a) Sitting in a chair

   Not at all breathless  Extremely breathless

   b) Walking around inside the house

   Not at all breathless  Extremely breathless

   c) Doing light housework

   Not at all breathless  Extremely breathless

   d) Walking on the flat outside the house

   Not at all breathless  Extremely breathless

   e) Going up hills outside the house

   Not at all breathless  Extremely breathless

   f) Walking upstairs in the house

   Not at all breathless  Extremely breathless

2. Generally, how was your breathlessness today?

   Not at all breathless  Extremely breathless

3. What was your appetite like today?

   No appetite at all  Excellent

4. How did you sleep last night?

   Not at all  Very well
References


Effets de la protriptyline sur l'insuffisance respiratoire chez les patients atteints de limitation chronique des débits aériens. N. Carroll, R.A. Parker, M.A. Branthwaite.

RÉSUMÉ: Le traitement de l'hypventilation nocturne chez les patients atteints d'un syndrome restrictif d'origine pulmonaire a été réalisée par l'emploi de protriptyline, qui réduit la durée du sommeil à mouvements oculaires rapides (REM) pendant les phases d'hypventilation nocturne. Dix-huit patients atteints d'une limitation sévère et chronique des débits aériens (CAL) ont participé à un essai randomisé, en double anonymat, avec permutation croisée de protriptyline et de placebo. L'étude a été complète chez 17 d'entre eux. L'emploi de protriptyline a entraîné une chute de la force des muscles respiratoires (p<0.05) et une augmentation de la distance de marche en 6' d'une moyenne de 258 m (extrêmes: 58.5-585 m) à 275 m (extrêmes: 171-598 m) (p<0.02). Le traitement pharmacologique de l'hypventilation nocturne du stade REM s'avère efficace chez les patients atteints de CAL, mais les effets anticholinergiques pourraient être utilisés en traitement au long cours, surtout chez les sujets âgés de sexe masculin. Eur Respir J., 1990, 3, 746-751.