Protriptyline treatment of sleep hypoxaemia in Duchenne muscular dystrophy

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ABSTRACT  Protriptyline 20 mg daily reduced the total time spent in rapid eye movement sleep in an open study in four subjects with Duchenne muscular dystrophy. Sleep related hypoxaemia and episodes of desaturation were reduced. Anticholinergic side effects were prominent, however, in these patients, precluding its use for regular treatment.

Introduction

Patients with very weak inspiratory muscles are vulnerable to recurrent hypoxaemia during rapid eye movement (REM) sleep, possibly as a result of the reduction in intercostal and accessory muscle activity that normally accompanies this sleep stage. Pharmacological suppression of REM sleep is a possible therapeutic approach to REM related hypoxaemia. Protriptyline, a non-sedating tricyclic antidepressant, has been used successfully for the treatment of classical sleep apnoea syndromes. We describe a short term open study of protriptyline in five patients with advanced Duchenne muscular dystrophy who had REM related hypoxaemia but described no abnormal sleep symptoms or hypersomnolence.

Methods

Five patients aged 18–21 (mean 18.8) years with Duchenne muscular dystrophy, but with minimal scoliosis and no abnormal sleep symptoms, entered the study. REM related sleep hypoxaemia (>10% oxygen desaturation) had been documented in all the subjects. Vital capacity (VC), maximum inspiratory (MIP) and expiratory (MEP) static mouth pressures, and arterial blood gas tensions were measured by standard methods. Standard polysomnography methods, with an acclimatisation night, were used. The patients were positioned and turned during the study as necessary by a parent, who slept nearby. No particular sleeping posture was imposed. After the baseline study the subjects were prescribed protriptyline 20 mg daily for 14 days, after which they were studied again with a further acclimatisation night. The drug was then discontinued. A symptom questionnaire was completed after the study.

Episodes of desaturation were classified as falls of at least 5% or 10% from the preceding stable (usually non-REM) value. Definitions of hypopnoea, apnoea, arousals, and awakenings and the criteria for sleep staging and heart rate estimation were as described previously. Mean (SEM) values were compared by Student’s t test and correlation between mean values for the different variables for each subject by regression analysis.

Results

Four patients completed the study. One 15 year old patient (VC 1.0 litre, MIP 30 cm H2O, MEP 20 cm H2O) withdrew before the second study with intolerable constipation and a thrombosed haemorrhoid after seven days. The four remaining patients also reported anticholinergic symptoms—dry mouth (three), constipation (three), micturition difficulty (two) blurred vision (one).

The mean (range) pulmonary function values of the four patients included: VC 1.0 (0.7–1.3) litre, MIP 31.3 (25–40) cm H2O and MEP 26.3 (15–40) cm H2O; when they were breathing air the arterial carbon dioxide tension (Paco2) was 5.5 (4.8–6.05) kPa and oxygen tension (Pao2) 14.2 (12.5–17.9) kPa. The table shows mean sleep times, the proportion and latency of REM sleep, oxygen saturation, characteristics of hypopnoea and apnoea, and frequency of arousals and awaken-
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Mean [range] (SEM) values from baseline and protriptyline sleep studies of the four patients: total sleep time (TST) and percentage of TST in stage REM (%SR); REM onset latency excluding periods of wakefulness (ROL excluding W); oxygen saturation (Sao,) awake and in non-REM sleep and desaturation frequencies per hour slept; episodes of hypopnoea or apnoea; arousal and awakening frequencies.

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Protriptyline</th>
</tr>
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<tbody>
<tr>
<td>TST (min)</td>
<td>388 [352–439]</td>
<td>412 [349–448]</td>
</tr>
<tr>
<td>% SR (%)</td>
<td>19.7 [14.9–29]</td>
<td>5.5 [0.0–12]</td>
</tr>
<tr>
<td>ROL (excluding W) (min)</td>
<td>106 [73–168]</td>
<td>&gt; 277 [198–&gt;349]</td>
</tr>
<tr>
<td>Sao, (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Awake</td>
<td>96.2 [95.5–97.0]</td>
<td>96.1 [95.0–98.0]</td>
</tr>
<tr>
<td>Non-REM sleep</td>
<td>94.5 [94.5–96.0]</td>
<td>95.5 [94.0–98.0]</td>
</tr>
<tr>
<td>No of desaturations/h</td>
<td>3.7 [1.4–16.1]</td>
<td>1.2 [0.2–8.8]</td>
</tr>
<tr>
<td>No of desaturations/h</td>
<td>3.2 [0.3–10.7]</td>
<td>0.4 [0.0–1.2]</td>
</tr>
<tr>
<td>Hypopnoea or apnoea</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total No of episodes</td>
<td>81.0 [18.9]</td>
<td>28.3 [12.3]*</td>
</tr>
<tr>
<td>Duration (s)</td>
<td>27.1 [2.6–5.0]</td>
<td>18.9 [2.2]*</td>
</tr>
<tr>
<td>Frequency/h</td>
<td>12.6 [2.9–3.0]</td>
<td>4.0 [1.8]*</td>
</tr>
<tr>
<td>Arousal frequency/h</td>
<td>12.4 [6.2–20.8]</td>
<td>9.3 [5.6–15.6]</td>
</tr>
<tr>
<td>Awakening frequency/h</td>
<td>0.9 [0.3–1.1]</td>
<td>0.9 [0.5–1.4]</td>
</tr>
</tbody>
</table>

*p < 0.05 for significance of differences between means.

ings for the four patients who were studied twice. Mean sleep efficiency (total sleep time (TST) as a proportion of the study duration) was similar on the baseline (76.4%) and protriptyline (79.9%) nights. The proportion of TST by REM sleep (%SR) was greatly reduced in three subjects but almost unchange-ged in one, the overall mean reduction being 67.3% (14.8–100%). The latency of onset (excluding awake time) of REM sleep was also greatly increased in three (no REM sleep being recorded in one of these) but little changed in one.

The figure illustrates typical suppression of REM
sleep and improvement in REM associated oxygen desaturation with protriptyline. One patient, who had REM related desaturation of over 10% in the baseline study, showed no REM sleep and no oxygen desaturation with protriptyline.

The proportion of total sleep occupied by hypopnoea or apnoea was reduced during protriptyline treatment in all patients by 45–95%, from a mean (SEM) % of 10·1 (3·1) to 2·6 (1·1) (p < 0·05). The extent of REM suppression was correlated with the percentage reduction in 5% desaturation frequency (r = 0·956 (p < 0·05)) and with the reduction in hypopnoea or apnoea with protriptyline (r = 0·997, p < 0·01). The frequency and duration of non-REM events also fell in all subjects having the treatment (baseline 3·98 events/hour REM none sleep (mean duration 23·4 seconds); protriptyline 1·57 events/hour non-REM (duration 15·6 s)).

The mean heart rate in stable non-REM sleep increased in all subjects during protriptyline treatment by 21–47% (mean 32·6%), from a mean of 75·8 to 99·6 beats/min. Similar changes were seen in REM sleep.

Discussion

Protriptyline was effective in suppressing REM sleep, thereby reducing oxygen desaturation and disordered breathing during sleep in three out of four subjects with advanced Duchenne muscular dystrophy. Unfavourable anticholinergic effects of protriptyline were seen, however, in all subjects, and led to the withdrawal of a fifth subject from the study.

The small number of patients and the short treatment period reflect the practical and ethical constraints of administering a poorly tolerated substance to very disabled patients with no complaints of abnormal sleep or somnolence. Despite similar acclimatisation for the two parts of the study, an “order effect” of treatment night following baseline night was inevitable; any order effect from improved acclimatisation should, however, increase the proportion of REM sleep from the first to the second studies, which was not seen. The extent of REM suppression varied widely among the four subjects. Serum protriptyline concentrations were not available, but the rise in sleeping heart rate in all subjects with treatment suggests that, despite side effects, the medication had been taken as prescribed.

Anticholinergic effects may be especially disadvantageous to people advanced disability, constipation being a particular problem in these patients with low expulsive ability and poor mobility. The increased heart rate and the tendency of tricyclic antidepressant drugs to precipitate arrhythmias may present a specific hazard to patients with Duchenne muscular dystrophy as they already have a high prevalence of electrocardiographic conduction abnormalities and cardiomypathy.

The main potential benefit of protriptyline to patients with sleep disordered breathing relates to its ability to suppress REM sleep, though suppression varies between individuals. Data from animals suggest that enhancement of efferent activity to the upper airway muscles by protriptyline may contribute to the relief of obstructive sleep apnoea, perhaps explaining the apparent influence of protriptyline in non-REM sleep, as observed in our subjects. Protriptyline has previously been used effectively in the treatment of patients with symptomatic obstructive sleep apnoea and in patients with cardiorespiratory failure from scoliosis or restrictive lung disease or both. Its reported use in patients with primary neuromuscular disease has been limited to isolated cases of myotonic dystrophy, postpoliomyelitis syndrome, and nemaline myopathy, with few details of polysomnographic studies. Its use in Duchenne muscular dystrophy has not previously been reported.

Although suppression of REM sleep improves both sleep disordered breathing and the associated hypoxaemia during sleep in Duchenne muscular dystrophy, protriptyline appears to be inappropriate for this purpose because of adverse anticholinergic effects; occasionally REM sleep may still occur normally despite such side effects. Suppression of REM sleep by a non-tricyclic agent may provide an alternative approach to treatment.

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