Modafinil for daytime somnolence in Parkinson’s disease: double blind, placebo controlled parallel trial

W G Ondo, R Fayle, F Atassi, J Jankovic


Methods

The Baylor College of Medicine institutional review board approved the protocol. We recruited patients meeting the diagnosis of PD from the Baylor College of Medicine Parkinson’s Disease Center and Movement Disorders Clinic. All subjects satisfied the diagnostic criteria for PD,24 were between 35 and 80 years of age, and reported daytime somnolence as measured by an ES score of greater than 10.25 Patients with serious medical conditions, known narcolepsy, known sleep apnoea, and pregnancy were excluded. The subjects were not allowed to take prescription stimulant medications.

We collected demographic data, including a composite dopaminergic dose using the formula: dose = levodopa/100 + controlled release levodopa/130 + pramipexole/1 + pergolide/0.75 + ropinirole/3.5. If entacapone or tolcapone was used, we increased the levodopa dose by 10%. Other PD medications were not included in the formula.

The primary efficacy point was a change in ES score, as we feel that this best captures the daytime sleep problems experienced by most patients with PD. Secondary endpoints included the Unified Parkinson’s Disease Rating Scale (UPDRS),26 the Fatigue Severity Scale,27 the Hamilton Depression Scale,28 global impressions, and the Medical Outcome Survey Short Form 36 (SF-36) Quality of Life scale.29 We also systematically assessed adverse events. The subjects also underwent a standard multiple sleep latency test (MSLT) in the morning (naps at 9 am, 11 am, 1 pm, 3 pm) at baseline and after treatment.30 Sleep onset was scored at the first epoch of any identifiable stage of sleep after lights out. Subjects also completed a sleep survey, including their subjective report of the previous nights. Those with motor fluctuations also completed a one day “on/off” diary just before starting the study drug and one day before their final evaluation. The UPDRS part III motor examinations were done in the “on” state. If subjects were fluctuators, the UPDRS part II activities of daily living scores were calculated by averaging the “on” and “off” scores.

Abbreviations: EDS, excessive daytime somnolence; ES, Epworth Sleepiness (score); MSLT, multiple sleep latency test; PD, Parkinson’s disease; UPDRS, Unified Parkinson’s Disease Rating Scale
After signing informed consent and baseline assessments including the MSLT, the subjects were randomised by a computerised randomisation code to receive either modafinil or placebo in a 1:1 ratio. Both the drug and the placebo, which matched the drug in taste and appearance, were supplied by Cephalon Inc. and distributed to the coordinator by another coordinator who was shielded from the subjects and not otherwise involved in the study in any way. The subjects began taking modafinil, one pill of 100 mg, or matching placebo, upon waking and at lunch (200 mg/day). After one week, the dose was increased to two pills twice a day (400 mg/day). One week later, we administered the ES that prevented his return), and one woman, who was on modafinil (who stopped due to instructions by her local physician to stop “study medication” because of back pain). All three dropped out prior to any post-drug evaluation. The remaining 37 patients completed all assessments.

There was no significant change in the primary endpoint, the ES score. Subjects on modafinil showed an improvement of 2.7 points compared with those on placebo who improved by 1.5 points (p = 0.28). MSLT results were not significantly different although the scores worsened less with modafinil (−0.16 (3.59) minutes) than with placebo (−0.70 (3.28) minutes), p = 0.14 (table 2). The UPDRS, Fatigue Severity Scale, Hamilton Depression Scale, SF-36, and global impression scores did not significantly change compared to baseline values. We analysed the change from baseline at all scheduled visits and last visit in the above mentioned efficacy variables using an analysis of covariance (ANCOVA) model with treatment and baseline values in the model. The proportion of Fatigue Severity Scale and global impression responders were analysed using a χ² test or Fisher’s exact test if warranted. The global impression response at the last visit was analysed using the Cochran–Mantel–Haenszel test.

RESULTS
There were no significant differences in any demographic or baseline variables between the subjects assigned to the study drug and placebo (table 1). Three subjects dropped out: two men, both of whom were taking placebo (one due to acute illness and subsequent death from acute myelogenous leukaemia and the other due to his spouse’s serious illness that prevented his return), and one woman, who was on modafinil (who stopped due to instructions by her local physician to stop “study medication” because of back pain). All three dropped out prior to any post-drug evaluation. The remaining 37 patients completed all assessments.

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We conducted a power analysis to determine the minimum sample size needed to detect a four point ES score difference between two groups. Based on the mean (SD) of qualifying subjects (ES>10) from our survey population of 303 patients with PD, we required a total of 18 (4 per group) participants to achieve a power of 0.81 at α = 0.05 (two tailed).

### Table 1 Demographic and entry data (n = 40)

<table>
<thead>
<tr>
<th></th>
<th>Modafinil (n = 20)</th>
<th>Placebo (n = 20)</th>
<th>Entire group (n = 40)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)*</td>
<td>64.4 (10.4)</td>
<td>65.1 (12.3)</td>
<td>64.8 (11.3)</td>
</tr>
<tr>
<td>Sex (men/women)</td>
<td>13/7</td>
<td>13/7</td>
<td>26/11</td>
</tr>
<tr>
<td>Duration of Parkinson’s disease*</td>
<td>6.5 (5.5)</td>
<td>7.0 (4.6)</td>
<td>6.8 (5.0)</td>
</tr>
<tr>
<td>Dopaminergic dose (mg/day)*</td>
<td>7.3 (3.5)</td>
<td>9.5 (5.2)</td>
<td>8.5 (4.6)</td>
</tr>
<tr>
<td>Fluctuating response</td>
<td>5/20</td>
<td>7/20</td>
<td>12/40</td>
</tr>
<tr>
<td>UPDRS activities of daily living</td>
<td>12.9 (5.5)</td>
<td>14.4 (6.0)</td>
<td>13.7 (5.8)</td>
</tr>
<tr>
<td>UPDRS motor*</td>
<td>24.1 (9.8)</td>
<td>29.2 (9.5)</td>
<td>26.7 (9.9)</td>
</tr>
<tr>
<td>Epworth score*</td>
<td>15.8 (3.0)</td>
<td>15.9 (3.5)</td>
<td>15.8 (3.2)</td>
</tr>
</tbody>
</table>

*Data are mean (SD).

UPDRS, Unified Parkinson’s Disease Rating Scale.

### Table 2 Efficacy data (n = 37)*

<table>
<thead>
<tr>
<th></th>
<th>Modafinil (n = 19)</th>
<th>Placebo (n = 18)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Visit 1</td>
<td>Visit 2</td>
</tr>
<tr>
<td>Epworth Scale</td>
<td>15.7 (3.1)</td>
<td>13.5 (4.8)</td>
</tr>
<tr>
<td>UPDRS activities of daily living</td>
<td>12.5 (5.4)</td>
<td>12.7 (5.6)</td>
</tr>
<tr>
<td>UPDRS motor</td>
<td>9.9 to 15.1</td>
<td>10.1 to 15.5</td>
</tr>
<tr>
<td>MSLT (mean minutes)</td>
<td>23.9 (10.0)</td>
<td>23.7 (9.5)</td>
</tr>
<tr>
<td>Fatigue Severity Scale</td>
<td>19.1 to 28.7</td>
<td>19.1 to 28.2</td>
</tr>
<tr>
<td>Hamilton Depression Scale</td>
<td>4.5 to 6.9</td>
<td>4.9 (3.6)</td>
</tr>
<tr>
<td>Change in sleepiness</td>
<td>6/19 (32%)</td>
<td>6/19</td>
</tr>
</tbody>
</table>

*Data are mean (SD) and 95% confidence intervals.

†None of the subsections of the SF-36 significantly improved compared with placebo.

All comparisons: p>0.05

UPDRS, Unified Parkinson’s Disease Rating Scale.
placebo. In fluctuating subjects, there was no change in on/off time (table 2).

The medication was well tolerated in our patients. Only one patient taking modafinil elected to return to the lower dose, secondary to nausea and anxiety. Other adverse events thought to be at least possibly related to drug included dry mouth (n = 1), dizziness (n = 1), and back pain (n = 1). Adverse events recorded in subjects taking placebo included hyponatremia requiring hospitalisation and reduction of antihypertensive medications (n = 1), renal calcinosis (n = 1), and blurred vision (n = 1).

DISCUSSION

This double blind, placebo controlled study of patients with PD failed to show a significant reduction of daytime somnolence as measured by ES, the primary endpoint. Secondary outcome measures such as MSLT, Fatigue Severity Scale, Hamilton Depression Scale, and global impression scores also showed no difference between modafinil and placebo. The PD motor status was not affected and adverse events were minimal.

These results contrast with the results of two other controlled trials that have reported significantly improved ES in patients with EDS associated with PD.20 21 Both trials were crossover, smaller, and of shorter duration, although Adler et al’s study was reanalysed as a parallel design using the first arm due to a large carry-over effect. Neither reported a power analysis. Patient demographics (age, sex ratio, duration of PD) were similar to our study, although baseline sleepiness was less severe in Hogl et al’s study.20 The dose of modafinil in both studies was actually lower than in ours. The actual improvement in ES on drug was 2.7 in our study, compared with 3.3 and 3.4 in the others. The placebo response was also slightly greater in our study resulting in a smaller overall treatment effect (1.2 in ours v 2.6 and 4.7 in the others). The greater placebo response may have resulted from the twice daily dosing.

The PD subjects enrolled in our study demonstrated marked EDS as determined by MSLT and ES. Both measures were similar in severity to those seen in narcolepsy patients.23 24 In contrast with narcolepsy, however, only four of our subjects demonstrated any early onset rapid eye movement period (EOREMP). In those four subjects, 9/32 nap opportunities (28%) resulted in EOREM. These findings concur with some other reports, which do not show EOREM20 21 but contrast with others that show moderate rates of EOREM, still lower than that seen with narcolepsy.3 13

Several other potential methodological issues related to our study should be addressed. Firstly, we are a tertiary referral centre and our PD patient population may differ from that in a primary care setting. Secondly, polysomnographic testing on the night before MSLT would have been ideal to better interpret the MSLT data and evaluate for sleep apnoea or other specific nocturnal problems that could affect daytime somnolence. Nevertheless, in our PD population, the subjective reports of the two groups regarding their previous night’s sleep were similar, and we have no reason to hypothesise that the two randomised groups would have had different polysomnogram results. The Maintenance of Wakefulness Test15 may have more sensitively captured a pharmacological intervention for wakefulness19; however, we felt that the MSLT best reflects the clinical scenario seen in PD. Furthermore, the only study that measured Maintenance of Wakefulness Test in PD patients also failed to show significant improvement with modafinil over placebo.20

Thirdly, employing a minimum cut-off of the primary variable (ES) in the exclusion criteria can result in artificial regression toward the mean. Three subjects on placebo reported a greater than five point improvement in ES. Our subjects only took 200 mg modafinil or placebo prior to their MSLT, as they took their second dose after its completion. Lastly, despite our power analysis, this was still a relatively small study and may suffer from type II error. It was also a short term study.

CONCLUSION

Our results do not support the efficacy of modafinil (400 mg/day in divided doses) for daytime somnolence in PD. The drug, however, was very well tolerated and has an immediate effect, and individual patients did benefit from taking it. Since the aetiology of excessive sleepiness is multifactorial, modafinil may be considered on an individual basis. Furthermore, the equipoise generated by mixed study results justifies additional trials.

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REFERENCES


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