Daytime sleep in Parkinson's disease measured by episodes of immobility

K. Kotschet a,b, W. Johnson b, S. McGregor b, J. Kettlewell a, A. Kyoong b, D.M. O'Driscoll c,d, A.R. Turton e, R.I. Griffiths a, M.K. Horne a,b,*

a Florey Institute for Neuroscience and Mental Health, University of Melbourne, Parkville 3010, Australia
b St Vincent's Hospital, Fitzroy, Victoria 3065, Australia
c Department of Respiratory and Sleep Medicine, Eastern Health, Victoria 3128, Australia
d Southern Clinical School, Monash University, Clayton, Victoria 3168, Australia
e Monash Lung and Sleep, Monash Health, Clayton, Victoria 3168, Australia

ARTICLE INFO
Article history:
Received 28 July 2013
Received in revised form
3 January 2014
Accepted 12 February 2014

Keywords:
Sleep
Actigraphy
Daytime sleepiness
Automated analysis
Parkinson's
Bradykinesia

ABSTRACT
Excessive daytime sleepiness (EDS) is common in Parkinson’s Disease (PD). Actigraphy uses periods of immobility as surrogate markers of nighttime sleep but there are no examples of its use in assessing EDS of PD. A commercial wrist worn system for measuring bradykinesia and dyskinesia also detects 2 min periods of immobility, which have a 85.2% concordance with the detection of sleep by ambulatory daytime polysomnography. (p < 0.0001 Chi Squared). High Epworth Sleepiness Scores (ESS) were associated with a proportion of time immobile (PTI) (p = 0.01 Mann–Whitney U). The median PTI between 0900 and 1800 h in 30 age matched control subjects was 2%, representing 10 min and PTI at or above the 75th percentile (5% or 27 min) was taken as a high level. PD patients had higher PTI (median 4.8%) than controls (p < 0.0001, Mann–Whitney U). PD subjects with a high PTI had more bradykinesia, less dyskinesia and higher PDQ39 scores than those with low PTI. There was no relationship between PTI and dose or type of PD medications. However, in 53% of subjects, PTI increased in the 30–60 min after levodopa confirming that in some subjects levodopa results in increased sleepiness. In summary, immobility is a surrogate marker of daytime sleep in PD, confirmed by correlation with PSG and ESS. PD subjects measured this way are more likely to be sleepy and sleepy PD subjects are more likely to be bradykinetic and have a higher PDQ39. Levodopa leads to an increase in sleepiness in more than half of subjects post dosing.

© 2014 Elsevier Ltd. All rights reserved.

1. Introduction
Excessive daytime sleepiness (EDS) is common in Parkinson’s Disease [1–4], occurring in 20–50% of subjects [3,5] and is considered to be present when the score from the Epworth Sleepiness Scale (ESS) is 10 or greater [6,7]. Anti-parkinsonian therapies may contribute to EDS [8], especially dopamine D2–D3 agonists [9–12], apomorphine [13] and levodopa monotherapy [10]. While the dose of antiparkinsonian medications was related to EDS in some studies [14,15], this has not been a universal finding [8,16–18]. Indeed, in some studies, higher levodopa doses have been associated with increased vigilance [8,18]. EDS may also be associated with severity of PD [5,15] and the evidence for a correlation with severity of striatal dopamine denervation has been summarized by Arnulf [5]. On the other hand, others claim that fatigue, rather than EDS, may correlate better with disease severity [19].

Night-time sleep deprivation and fragmentation caused by nocturnal motor symptoms, sleep apnea, periodic leg movements, REM sleep behavioral disorder or disruption to the sleep–wake system [2,20] also contribute to EDS in PD. These night time factors have received greater attention than EDS itself, in part because studying EDS in PD is hampered by existing methods of detection which are largely based on self/spouse reporting through diaries or other subjective measures. Under reporting is common, with more than one third of PD patients failing to perceive daytime naps lasting minutes and involving slow wave sleep [21]. While daytime polysomnography (PSG) accurately measures sleep state, the
equipment lacks practicality in the optimal recording environment of normal daily activities. Multiple Sleep Latency Testing (MSLT) is also used to measure daytime sleepiness but also does not assess subjects in a naturalistic setting and does not always correlate with ESS [22]. While absence of movement, as measured for example by actigraphy, has proved to be a good proxy of night time sleep quality and correlates with PSG and subjective sleep measures [23], there are no studies that use it to measure daytime sleep in PD.

Recently, we described a system consisting of algorithms that operate on wrist accelerometer obtained in an ambulatory setting to quantify bradykinesia and dyskinesia (the Parkinson’s Kinetigraph or PKG, Global Kinetics Corporation) [24]. During these recordings, many PD subjects had episodes of complete immobility. The PKG produces scores every 2 min, representing the briefest of these episodes, but some were prolonged (i.e. hours). On direct questioning of subjects and spouses, the most important reason for immobility appeared to be daytime drowsiness or sleep. While the PKG is similar to actigraphy in using accelerometry to detect absence of movement [25], it differs by providing simultaneous measures of bradykinesia and dyskinesia over the recording period and by recording the timing of levodopa consumption. Thus, the PKG provides the opportunity of linking these episodes of immobility to bradykinesia, dyskinesia and PD medications.

2. Methods

Subjects with idiopathic levodopa responsive PD were recruited from the Movement Disorder Clinic at St Vincent’s Hospital. Control subjects were recruited from the spouses of PD subjects. The study was approved by the St Vincent’s Health Human Research & Ethics Committee. All subjects provided consent. Control subjects all wore the PKG and 10 also had Hess performed. All PD subjects wore the PKG and had Hess scores, UPDRS III motor scores and daily levodopa equivalent dose (LED) recorded. A significant but variable proportion of PD patients also had modified Abnormal Involuntary Movements (AIMS), PDQ39 and Addenbrooke’s Cognitive Examination (ACE) scores. All clinical rating scales were performed in the “on state” prior to wearing the PKG.

2.1. Recording protocol

The PKG system was used to provide bradykinesia and dyskinesia scores (BKS and DKS respectively) [24]. This device is worn on the wrist of the most severely affected side and contains a rechargeable battery, a triaxial accelerometer, memory, a reminder of medications due, a means for recording when medications were taken, as well as a capacitive sensor to detect removal from the wrist. Subjects wore the device for 10 consecutive days, from first arising until retiring at night, except when washing. At the end of the recording period, data was downloaded and analyzed using a proprietary algorithm to calculate BKS and DKS [24]. The BKS and DKS are continuous variables. In the case of the BKS, the scores can range from movements that are made with normal acceleration to those that have very low or no acceleration. The correlation between BKS and DKS and conventional clinical rating scales has been discussed elsewhere [24].

2.2. Identification of immobility by the PKG

Ten day PKG recordings provided BKS and DKS every 2 min and Fig. 1 provides examples of day long recordings from a control and 2 PD subjects. On inspection of Fig. 1A, B, C it was apparent that some BKS were very low (< ~80, highlighted by beige band). According to the sensor in the PKG, the device was being worn at these times, but the output of the accelerometer indicated that the subject was completely motionless and so the episodes were called episodes of immobility (Fig. 1). Thus Episodes of Immobility were of 2 min or greater in duration and with BKS that were at or below the threshold of ~80 BKS. These Episodes of Immobility were removed from all subsequent assessments of BKS and DKS used to represent bradykinesia and dyskinesia in these subjects.

2.3. Method for ambulatory daytime polysomnography (PSG)

Ambulatory PSG was performed using a Philips Respironics Alice PDx device for data acquisition. Using a modified montage only acquiring a frontal EEG signal (references to A1/A2 depending on application point) and a single lead ECG. Recordings were made from 900 h to 1930 h on 3 PD subjects. The data was analyzed using Respirics SleepWare G3 version 3.3.3 software and 30 epochs were scored for sleep presence, focusing mainly on stages N1–N3 (non REM sleep), according to the AATA/ASA guidelines for the Scoring of Sleep issued in 2010 [20]. No REM sleep was observed. As the PKG provides a BKS every 2 min and the PSG provides a sleep score every 30 s, the PSG was reduced to single score over the 2 min to allow the PKG and PSG to be compared. If two or more 30 s PSG epochs in a 2 min PKG epoch were “positive” for sleep, then the PSG was taken as reporting “sleep” for that 2 min period.

3. Results

PKG recordings were obtained from 68 PD patients aged 40–80 years (median 65.9), with disease duration from 6 months to 25 years (mean 8.7 years), LED (median 895, interquartile range: 400–431) and UPDRS III scores ranging from 4 to 53 (mean 25.9). There were 30 controls, aged 50–84 years (mean 65.8), and 10 of these who were matched for age (range 56–82 years: mean 68) also had an ESS performed.

3.1. Periods of immobility as a measure of daytime sleep

Epochs of immobility (see Methods) last 2 min and would qualify as a period of sleep when measured by actigraphy [25] and appeared to coincide with sleep in our study. For example, examination of Fig. 1F suggests this subject awoke most days about 0630 h and retiring about 2000 h, and immobility (suggesting sleep) is almost continuous before and after these times respectively. It is unlikely that most epochs of immobility represents severe bradykinesia because in many cases (e.g. subject in Fig. 1F) these periods last for >10 min, occur immediately alongside periods of much lesser bradykinesia severity, occur in controls (albeit less frequently) and importantly the subject and/or their spouses reported that they are explained by somnolence or sleep. Because the time interval of interest will vary, the proportion of time immobile (PTI) will be used. For example, the period between 0900 and 1800 is 540 min, and so the case in Fig. 1B and E had 32 min of PTI, representing a PTI of 6%.

Daytime ambulatory PSG was performed on 7 PD subjects whose time immobile, measured on a previous PKG recording were greater than 30 min/day. PSG and PKG were recorded simultaneously from ~0900 h until 1930 h, with ~250 two minute epochs/patient and thus a total 1805 two min epochs for analyses. Fig. 1G is a graphical representation of the presence (+) or absence (−) of immobility (PKG score) and sleep (PSG score) for each subject. There was concordance between immobility and PSG scores in 85.6% of the 1805 two minute epochs: 1206 epochs were negative for sleep by both methods and 342 epochs were positive for sleep by both methods (p < 0.0001, Chi Squared test). The Kappa statistic for the concordance of the two methods was 0.63 and the Sensitivity was 0.83 and Selectivity was 0.89. Two thirds (167) of the discordant epochs occurred when immobility was detected by PKG but not by PSG. Discordant epochs (brown and green lines in Fig. 1G) tended to cluster around periods when both methods were also likely to detect immobility and sleep (red lines in Fig. 1G).

The other widely accepted marker of EDS is the ESS. Those PD patients with an ESS of 10 or greater, which is considered “high” and consistent with EDS [6,7], had significantly higher PTI than subjects with a low ESS (p = 0.01 Mann–Whitney U, Fig. 2A and C). Thus, in a manner similar to actigraphy, immobility detected by the PKG is a surrogate marker of sleep. We therefore exploited the advantages provided by the PKG of comparing bradykinesia, dyskinesia and the consumption of medication using immobility as a marker of daytime sleep.

3.2. Daytime sleepiness in PD

The median PTI of 30 controls was 2.0 (interquartile range 1.2–5.0, Fig. 2B). In the 10 controls who also had ESS performed, the...
median PTI was also 2.0 (interquartile range 1.4–5.3) and their median ESS was 3 (interquartile range 1–7). In PD subjects, the median PTI was 4.8 (interquartile range 2.0–10.2), which was significantly different from the 30 controls (p < 0.0001, Mann–Whitney U). EDS is common in the general older population and examination of the distribution of PTI in controls (Fig 2B) even hints at a bimodal distribution with a small inflection around 6%. Subjects whose PTI was 5.0 or greater (i.e. above the 75th percentile of controls, Fig 2B), which represents 27 min of immobility over period 900 h and 1800 h, were considered to have a “high” PTI in subsequent analyses. PD subjects whose PTI was greater than this had a significantly higher ESS than those with a low PTI (p < 0.001 Mann–Whitney U) (Fig 2D).

3.3 Sleepiness and measures of PD

PD patients with a low PTI had significantly less bradykinesia, as measured by the BKS than those with a high PTI (mean 19.8 v 25.9, p < 0.0001, Table 1). Note that all episodes where the BKS was ≥80 were excluded when estimating bradykinesia using the BKS. There was trend for similar differences in UPDRS III (mean 27.2 v 23.1) that just failed to reach statistical significance (Table 1). On the other hand, dyskinesia measured by the DKS was higher in those patients with low PTI than in those whose PTI was high (mean 10 v 3.3, p < 0.0001, Table 1). There was trend for similar differences in AIMS (4.6 v 7.7) for high and low PTI respectively, that just failed to reach statistical significance.

Some of 68 PD subjects also had PDQ39 (28) and ACE (41) performed (Table 1). The mean PDQ39 in those patients with low PTI was about two thirds of the mean of those with high PTI (36 vs 55), but this was not significant (most likely because of the small numbers of subjects with a high PTI who had also had a PDQ39 performed). There was no difference in the mean ACE score of the low and high PTI groups.

3.4 Influence of PD medications on PTI

There was no relationship between LED and a high or low PTI in the 68 PD subjects (Table 1). However, it is common clinical experience that some patients become sleepy after a dose of levodopa and this pattern was observed in some subjects (e.g. Figs. 1B and 3A). The relationship between levodopa dosing and immobility was examined in 26 PD subjects prescribed between 3 and 5 daily levodopa doses daily. These subjects took 81 levodopa doses in the period between 900 h and 1800 h (chosen as a period when most subjects would be out of bed and active). The median PTI in the 30 min before each of these doses (“before”) and the 30–60 min “after” each dose (allowing time for gut absorption of levodopa) was calculated (Fig 3A). The median “before” PTI was 6.7%, corresponding to 2 min over the 30 min period. The effect of levodopa on...
sleepiness was examined by subtracting the PTI “after” from the PTI “before” for each dose (PTI\(_{A/C0B}\) if levodopa increased sleepiness then PTI\(_{A/C0B}\) would be > 0 (Fig 3B and C). In 53% of doses PTI\(_{A/C0B}\) was > 0 and for 33% it was < 0 (p < 0.01, Fishers Exact). While the mean increase in PTI is small (1.1%), in about 25% of subjects PTI increased by 6% (~2 min over 30 min). Note that this infers time asleep and drowsiness may be overlooked. The relationship between post levodopa somnolence and background somnolence was examined by plotting the PTI “before” (as a representation of somnolence when effect of medications were lowest) against PTI\(_{A/C0B}\) (Fig 3D). This showed that subjects with low PTI (< 5.0%) before dosing were more likely to have increased PTI subsequent to levodopa dosing (PTI\(_{A/C0B}\) was positive in 22 of 30 instances). The median increase in PTI was 4%, although the increase was 7.3% or more in 25% of patients with a low PTI. On the other hand, those subjects whose PTI before dosing was high (≥ 5.0%), were more likely to experience some arousal post dosing (PTI\(_{A/C0B}\) was negative in 30 of 51 doses, with a median decrease of 4.0%). The statistics support the assertion that patients with a low background PTI are likely to have increased somnolence after a dose of levodopa, whereas patients with a high background PTI will not (p < 0.0001, Fishers Exact). Those with increased PTI “before” did not take more frequent levodopa doses or have higher individual doses, nor was there a significant trend in this direction. Subjects with a high PTI were not more likely to take D2 agonists. Subjects with a low BKS (< 27, the 75th percentile of controls, lesser bradykinesia) had a similar distribution of PTI\(_{A/C0B}\) as those with a high BKS ≥ 27. Thus, increased PTI post levodopa was not due to the level of treatment or responsiveness to medication.

4. Discussion

This study is in keeping with previous reports that immobility, measured by accelerometry, is a useful surrogate marker of sleep. There are few studies using this approach to measure daytime sleepiness, and this is the first to our knowledge that use it to assess daytime sleepiness in PD. The strong concordance between immobility and daytime ambulatory PSG argues that immobility does indicate episodes of daytime sleep or somnolence. It is likely that discordant epochs when immobility was present but the PSG

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Age and scores from clinical rating scales in 68 PD subjects with high or low PTI.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Low PTI (&lt;5.0)</td>
</tr>
<tr>
<td>No.</td>
<td>Mean</td>
</tr>
<tr>
<td>Age</td>
<td>33</td>
</tr>
<tr>
<td>DD</td>
<td>19</td>
</tr>
<tr>
<td>MedBKS</td>
<td>35</td>
</tr>
<tr>
<td>UPDRS 3</td>
<td>33</td>
</tr>
<tr>
<td>MedDKS</td>
<td>33</td>
</tr>
<tr>
<td>AIMS</td>
<td>26</td>
</tr>
<tr>
<td>ESS</td>
<td>33</td>
</tr>
<tr>
<td>BP ESS</td>
<td>8</td>
</tr>
<tr>
<td>LED</td>
<td>31</td>
</tr>
<tr>
<td>PDQ39</td>
<td>20</td>
</tr>
<tr>
<td>ACE-RA</td>
<td>18</td>
</tr>
</tbody>
</table>

DD, disease duration; AIMS, abnormal involuntary movements; MedBKS or DKS, median BKS or DKS; BP ESS, bed partner ESS; LED, levodopa equivalent dose; ACE-RA, Addenbrooke’s Cognitive Assessments Revised Australia.
did not show sleep represent somnolence, and if so, periods of somnolence that cause 2 min of immobility are likely to be clinical relevant. It is relevant that these periods of immobility were clustered close to other periods where both methods detected sleep. We also know that the PKG was being worn during PTI, because of the capacitive sensors in the device. We consider it unlikely that these episodes of immobility represent severe bradykinesia because in many cases (e.g. subject in Fig 1C and F), these periods last for >10 min, occur alongside periods where the BKS is of much lesser severity and also occur in controls (albeit less frequently). This study shows that PD patients are sleepier than age matched controls, using either the ESS or PTI as a marker of sleep and confirms previous findings using the ESS. However, while there are similarities with actigraphy in its method for measuring sleep, the PKG also has measures of bradykinesia and dyskinesia. It shows that sleepy PD patients, measured by immobility, are more bradykinetic and less dyskinetic. It is likely that a larger sample would have provided statistical support for impaired quality of life, measured by the PDQ39, in sleepy patients.

PD patients with greater EDS, measured by a high PTI, did not take higher dose of levodopa or were not more likely to take D2 agonists. While some have reported that the levodopa equivalent dose is associated with EDS [14,15], others have not found this association [8,16–18]. However, this study provides evidence that in some PD subjects, individual levodopa doses cause sleepiness, as measured by an increase in PTI. We can exclude the possibility that some of these events may be a transient worsening of symptoms soon after medication dosing (a ‘super-off’). These subjects were likely to be less sleepy overall, as measured by a low PTI. These findings suggest that those with PD who are not intrinsically somnolent may be more prone to treatment related somnolence. On the other hand, levodopa may increase arousal in those PD patients who have a high background PTI. The effect of dopaminergic medication on alertness is not straightforward and many dopaminergic agents, including levodopa, can have an effect on alertness [27–29] either by their direct action on dopaminergic receptors and transporters or indirectly through other transmitter systems [30]. The effects of exogenous dopaminergic pharmacologic stimulation on alertness may relate to both dosage (reviewed

**Fig. 3.** A: An example of a PD patient who tends to sleepiness, as measured by PTI, in the period after a dose of levodopa. The time of day is shown along the X axis and each of the 10 days of recording is shown on the Y axis. The heavy black lines indicate periods of immobility and the vertical red lines show when medication was due. The regions shaded in brown show the 30 min before and after a dose used in the analysis below. B: Frequency histogram of the PTI in the 30 min prior to each levodopa dose. The X axis shows both the PTI and the number of minutes of immobility represented by this. C: Frequency histogram for 81 individual levodopa doses, showing the change in PTI that occurred after levodopa dosing (PTI before along the X axis). There was a significantly greater PTI after a dose than before (see text for statistics). D: A plot of change post-levodopa dosing (PTI before) for PD patients whose PTI in the 30 min prior to medication was either low (<5.0) or high (>5.0). If medication had no effect on PTI, the score would be zero. This shows that subjects with low PTI before medication were more likely to have increased immobility post dose, whereas those with high levels of immobility prior to medications were more likely to have low PTI (see text).
by Rye [29]) and class of drug [8]. In animals, lower doses of many dopaminergic agents, including levodopa are soporific, mostly likely acting through the D1 and possibly D3 receptor, whereas at higher doses it enhances wakefulness. In humans, the effects on somnolence and alertness may also be dose and class dependent [8]. While others note that higher levels of levodopa increase alertness [8], we did not observe a relationship between dose of levodopa and post dose somnolence. Rather, the alerting effects of levodopa was predicted best by pre-dose level of somnolence (as measured by immobility). This suggests that underlying effects of alertness [8], we did not observe a relationship between dose of dopaminergic agents, including levodopa are soporific, mostly by Rye [29]) and class of drug [8]. In animals, lower doses of many

daytime sleep or at least somnolence in PD patients, and show that PD patients are more sleepy than controls, are more bradykinetic when PTI scores are high and that sleep or somnolence follows a dose of levodopa in some PD subjects. Future studies using this technique could address the relationship between night time sleep patterns and EDS in PD.

5. Conclusion

We argue that PTI, measured by the PKG, is a useful surrogate measure of daytime sleep or at least somnolence in PD patients, and show that PD patients are more sleepy than controls, are more bradykinetic when PTI scores are high and that sleep or somnolence follows a dose of levodopa in some PD subjects. Future studies using this technique could address the relationship between night time sleep patterns and EDS in PD.

Acknowledgments

 Funding was provided by the Medical Research Council Funds and by funds from Global Kinetics Corporation towards the salary of S. Osborn. Malcolm Horne is a Medical Practitioner Fellow supported by the National Health and Medical Research Council of Australia. K. Kotschet, R. Griffiths and M. Horne all have a pecuniary interest in Global Kinetics Corporation.

References


Please cite this article in press as: Kotschet K, et al., Daytime sleep in Parkinson’s disease measured by episodes of immobility, Parkinsonism and Related Disorders (2014), http://dx.doi.org/10.1016/j.parkreldis.2014.02.011