Z Gerontol Geriat 40:178–184 (2007)
DOI 10.1007/s00391-007-0420-z

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Actigraphy in agitated patients with dementia

Monitoring treatment outcomes

Aktometrisches Monitoring von Behandlungsverläufen Demenzkranker

▶ **Abstract** Especially in pharmacotherapeutic research, a variety of methods to monitor behavioural and psychological symptoms of dementia (BPSD) are currently being discussed. To date, the most frequently used of these are clinical scales, which, however, are subjective and highly dependent on personnel resources. In our study, we tested the usefulness of actigraphy as a more direct and objective way to measure day-night rhythm disturbances and agitated behaviour.

After a baseline assessment, 24 patients with probable dementia of the Alzheimer type (NINCDS-ADRDA) and agitated behaviour received either 3 mg melatonin (n = 7), 2.5 mg dronabinol (n = 7), or placebo (n = 10) for two weeks. In addition, 10 young and 10 elderly healthy subjects were examined as a control group. Motor activity levels were assessed using an actigraph worn continuously on the wrist of the non-dominant hand. At the beginning and the end of the study, patients' Neuropsychiatric Inventory (NPI) scores were also assessed.

In the verum group, actigraphic nocturnal activity ($P = 0.001$), NPI total score ($P = 0.043$), and NPI agitation subscale score ($P = 0.032$) showed significant reductions compared to baseline. The treatment-baseline ratio of nocturnal activity ($P = 0.021$) and treatment-baseline difference of the nocturnal portion of 24 h activity ($P = 0.012$) were reduced. Patients' baseline activity levels were similar to those seen in healthy elderly subjects. Younger healthy subjects exhibited higher motor activity even at night. There was no correlation between actigraphy and NPI.

Both actigraphic measures and the gold standard clinical scale were able to distinguish between the verum and placebo groups. However, because they did not correlate with each other, they clearly represent different aspects of BPSD, each of which reacts differently to therapy. As a result, actigraphy may well come to play an important role in monitoring treatment success in BPSD.

▶ **Key words** Actigraphy – age – agitation – Alzheimer's disease – behavioural and psychological symptoms of dementia (BPSD)

▶ **Zusammenfassung** Zur Dokumentation von Behandlungsverläufen bei Demenzpatienten mit nicht-kognitiver Symptomatik (behavioural and psychological symptoms of dementia, BPRS) werden verschiedene Methoden diskutiert. Derzeit werden vor allem klinische Skalen und psychometrische Tests angewandt, die subjektiv und personalaufwändig sind. Mit der vorgelegten Arbeit wollen wir zeigen, dass die Aktometrie als objektive Methode zur Aufzeichnung von agitiertem Verhalten und Tag-Nacht Rhythmusstörungen geeignet ist.

24 Patienten mit der wahrscheinlichen Diagnose einer Alzheimerdemenz (NINCDS-

Received: 15 December 2005
Accepted: 30 October 2006

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ADRDA) wurden eingeschlossen. Außerdem untersuchten wir 10 jüngere und 10 ältere gesunde Probanden. Nach einer interventionsfreien Beobachtungsphase erhielten die Patienten über einen Zeitraum 2 Wochen 3 mg Melatonin (n = 7), 2,5 mg Dronabinol (n = 7) oder Placebo (n = 10). Die motorische Aktivität wurde kontinuierlich mit einem Aktometer aufgezeichnet. Zu Beginn und am Ende der Beobachtungszeit wurde außerdem das Neuropsychiatrische Inventar (NPI) erhoben.

Die nächtliche aktometrische Aktivität (P = 0,001), der NPI-Gesamtscore (P = 0,043) und der NPI-Teilscore für Agitation (P = 0,032) waren in der Verumgruppe im Vergleich zu den Ausgangswerten signifikant erniedrigt. Das Behandlungs-Ausgangswert-Verhältnis der nächtlichen Aktivität (P = 0,021) und die Behandlungs-Ausgangswert-Differenz des Anteils der Nachtaktivität an der Gesamtaktivität (P = 0,012) zeigten eine deutliche Absenkung in der Verumgruppe im Vergleich zur Placebogruppe. In unbehandeltem Zustand zeigten die agitierten Patienten das gleiche Aktivitätsniveau wie die älteren Probanden. Die jüngeren Probanden hatten ein höheres nächtliches Aktivitätsniveau. Es gab keinerlei Korrelationen zwischen den aktometrischen Werten und dem NPI.

Sowohl für die aktometrischen als auch für die NPI-Daten zeigten sich Unterschiede in der Verum- und Placebogruppe. Da beide Methoden jedoch nicht miteinander korrelierten, folgern wir daraus, dass verschiedene, unabhängige Aspekte agitierten Verhaltens abgebildet wurden, die bei den Individuen unterschiedlich auf die Therapieversuche ansprachen. Damit hat die Aktometrie neben den klinischen Skalen einen wichtigen Stellenwert in der Dokumentation dieser Störungen.

Schlüsselwörter Aktometrie – Alter – Agitation – Alzheimerdemenz – Tag-Nacht-Rhythmusstörung

Introduction

Late in the course of Alzheimer's disease (AD), behavioural and psychological symptoms of dementia (BPSD) represent a major challenge in patient care [18, 30]. In particular, disturbed behaviour such as day-night rhythm disturbances and agitation can become a great burden to professional caregivers and family members alike [3]. Approximately half of patients with severe AD suffer from reduced amplitude of the day-night motor activity rhythm accompanied by increased activity levels at night, diurnal fatigue, and frequent daytime sleeping [24]. In fact, these symptoms are the number one cause of long-term hospitalisation in patients who suffer from AD [13]. Effective treatment strategies are lacking. As a result, BPSD has increasingly become the topic of pharmacological or other therapeutic research over the past several years [28].

In order to monitor changes in BPSD, clinical and nursing home staff, family members, and other caregivers commonly use rating scales or psychometric tests to assess disturbing symptoms such as depression, hallucinations, and agitation, or to evaluate more sophisticated constructions, such as quality of life or activities of daily living.

There are a number of clinical scales for measuring specific behavioural disturbances, such as the BEHAVE-AD scale [23] or the Cohen-Mansfield Agitation Inventory [5]. A variety of additional inventories contain specific subscales, such as the Neuropsychiatric Inventory (NPI) [6], Alzheimer Disease Assessment Scale (ADAS-noncog) [19], Gottfries-Brane-Steen Scale [4], and the Nurses' Observation Scale for Geriatric Patients NOSGER [26]. Nevertheless, all rating scales are subject to a certain degree of subjectivity.

In contrast, actigraphy allows motor behaviour to be quantified in an objective and highly effective manner in human psychopharmacology [20, 27]. It is inexpensive, non-invasive, and can be used over long periods of time (i.e. several weeks [22]). Actigraphy is frequently used to determine the rest-activity cycle in studies of insomnia, especially in the elderly [21] and in AD patients [12] and to evaluate effects of bright light treatment [2, 7, 8, 10]. Despite this, only a few pharmacological studies to date have used actigraphy to monitor behavioural disturbances in AD patients [15, 16, 25, 29]. The aim of our investigation was thus twofold: 1) to determine whether healthy subjects can be distinguished from AD patients by measuring motor activity actigraphically and 2) to test the usefulness of actimetry over the course of treatment as compared to clinical scales.

Method

Subjects

A total of 24 patients from our geriatric psychiatry unit who had been diagnosed with probable dementia of the Alzheimer type according to the NINCDS-ADRDA criteria [17] and were suffering from agitated behaviour were included in the study. Addi-

Table 1 Age and gender of subjects

	Verum	Placebo	Healthy younger	Healthy elderly
Number	14	10	10	10
Female	8	6	5	5
Male	6	4	5	5
Mean age (SD) [years]	79.0 (9,0)	78.2 (10.3)	22.6 (1.0)	84.3 (4.2)

tionally, 10 young and 10 elderly healthy subjects were included as a control group. Age and gender for all groups are provided in Table 1.

Patients were originally recruited for two pharmacological treatment studies [15, 31] on agitated behaviour in AD, both of which used the study design described here. Inclusion criteria were agitated behaviour, stable clinical state, and written informed consent by the patient and/or legal caregiver. Exclusion criteria were delirium, major depressive episode, suicidal tendencies, or any other severe somatic or psychiatric disturbances. Any medication used by the patients prior to the trial was kept unchanged. Preexistent medication with cholinesterase inhibitors or memantine was unchanged for at least four weeks prior baseline and during the entire course of the study.

Healthy subjects were recruited from a European sleep laboratory database study [14]. They were excluded if they showed any evidence of neurological, psychiatric, or somatic diseases as determined by clinical and psychiatric interviews, a physical examination, or routine blood and urine tests. They also had been free of any medication for at least four weeks prior to study entry. Participants completed the Mini Mental State Examination [9] (MMSE, exclusion if <25) and gave written informed consent.

Study design

All study procedures were approved by the ethics committee of the Charité University Medical Center in Berlin, Germany. Patients were assigned either to one of the two verum groups or to the placebo group. After two days of baseline assessment (melatonin group: seven days), patients received every evening either 3 mg melatonin (n=7), or 2.5 mg of the cannabinoid dronabinol (n=7) or placebo (n=10) for two weeks. Additionally, lorazepam 1 mg, clomethiazole 250 mg, or pipamperone 40 mg were administered to all patients as elective medication up to 3 times per day, as needed. Each dose was counted as one unit of additional medication.

Measurements

Motor activity levels were assessed continuously in all patients during the baseline and treatment periods (healthy subjects: for 14 days) using an actigraph worn continuously on the wrist of their non-dominant hand (Actiwatch, Cambridge Neurotechnology Co.). The actigraph uses an accelerometer, which produces voltage when the device is moved. Within the sensor, the degree and force of all movements are processed into activity counts, which are then recorded. Movement counts were performed every minute for the entire length of the trial. At baseline and at the end of the treatment period, patients were evaluated using the Neuropsychiatric Inventory (NPI) [6]. All ratings were made by one non-blinded investigator (SW).

Data processing and statistics

Raw data were processed using SLEEPWATCH® and EXCEL®. Motor activity counts per hour were calculated both for a 24 h and a nocturnal period (9 PM–6 AM) [11]. Parameters were calculated as the mean value of the last five days of the intervention period and the two days at baseline. Correspondingly, in healthy subjects the last five days were compared to the first two days.

Primary outcome measures were actigraphic nocturnal activity (AA_n) and actigraphic 24 h activity counts (AA_{24}). As a marker of any change over the course of treatment, the individual treatment-baseline ratio for nocturnal activity (AA_n ratio) and treatment-baseline differences in the nocturnal portion of 24 h activity (delta P_n) were calculated for the verum, placebo, elderly, and younger proband groups.

Additionally, the NPI total score and NPI subscore for agitation were calculated for all groups. Treatment-baseline ratio for these scales were correlated to the AA_n ratio and delta P_n.

Significant differences were explored within all groups using the Kruskal-Wallis test, and between the verum and placebo group using Mann-Whitney test. Changes from baseline to treatment condition were detected using the Wilcoxon test. For correlations, Spearman rho was calculated. The level of two-tailed significance was set at $P<0.05$.

Results

Median and range for all actigraphic data and NPI are given in Table 2. Compared to baseline, nocturnal activity (AA_n) was significantly reduced in the

Table 2 Actigraphic and clinical scale data in younger and elderly healthy subjects and for verum and placebo group under baseline and treatment conditions

a) Cross-sectional parameters (median, range)						
	Verum		Placebo		Healthy younger subjects	Healthy elderly subjects
	Baseline	Treatment	Baseline	Treatment		
NPI [1]	59 (16–91)	26 (16–50) [a]	54.5 (24–76)	34 (8–69)	–	–
NPI-agit [2]	10 (0–12)	3.5 (0–12) [a]	12 (0–12)	8 (0–12)	–	–
AA_n [3]	35.2 (19.9–80.1)	18.0 (3.8–38.0) [b]	20.5 (4.1–160.6)	34.4 (9.4–80.3)	52.2 (12.5–111.7)	31.4 (4.3–87.7)
AA_{24} [4]	76.1 (42.3–250.5)	53.1 (20.7–202.4)	111.4 (29.3–258.5)	112.9 (34.5–306.8)	179.2 (97.1–288.0)	120.4 (26.3–328.7)
b) Time course parameters (median, range)						
	Verum		Placebo		Healthy younger subjects	Healthy elderly subjects
NPI% [1,5]	56.9 (35–100)		70.8 (33–180)		–	–
NPI-agit% [2,5]	37.5 (33–100) [c]		100 (50–150)		–	–
AA_n ratio [3,5]	0.58 (0.15–0.93) [c]		1.01 (0.50–3.32)		1.02 (0.61–1.87)	1.09 (0.28–1.67)
Delta-P_n [6]	–0.15 (–0.36–0.2 [d]) [c]		–0.06 (–0.17–0.25 [3])		0.02 (–0.26–0.18 [3])	0.02 (–0.45–0.18 [3])

[1] Neuropsychiatric Inventory: total score; [2] Neuropsychiatric Inventory: subscore agitation; [3] Nocturnal actigraphic activity; counts per hour [100]; [4] 24h-actigraphic activity; counts per hour [100]; [5] Treatment/baseline value [%]; [6] Treatment-baseline difference of nocturnal portion of 24h-activity [%]; [a] vs baseline: significant $P<0.05$; [b] vs baseline: significant $P<0.01$; [c] vs placebo: significant $P<0.05$; [d] sic!

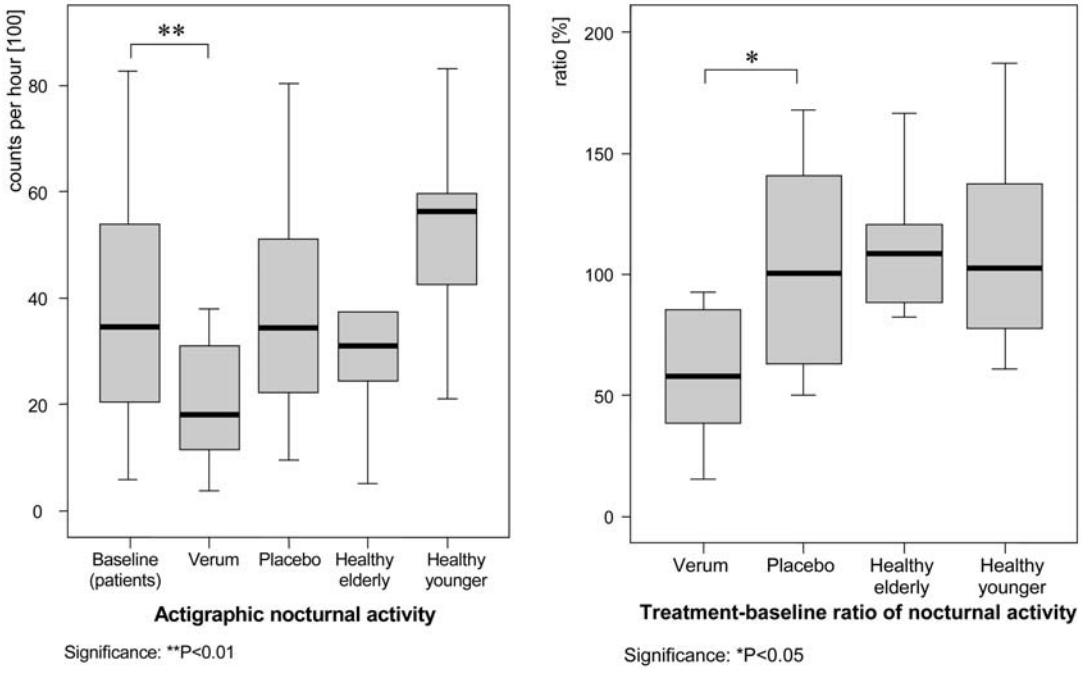

Fig. 1 Actigraphic outcome parameter (median, 25th and 75th percentiles, minimum, maximum) for healthy subjects and patients at baseline and under treatment conditions: **a** actigraphic nocturnal activity (AA_n), **b** treatment-baseline ratio of nocturnal activity (AA_n ratio)

verum group (Wilcoxon $Z=-3.18$; $P=0.001$, Fig. 1 a). However, differences in 24 h activity only tended toward significance. Correspondingly, NPI total score ($Z=-2.02$; $P=0.043$) and NPI agitation subscale ($Z=-2.14$; $P=0.032$) were reduced in the verum group. No changes were detectable for any of the four parameters in the placebo group compared to baseline.

The treatment-baseline ratio of nocturnal activity (AA_n ratio) as an actigraphic parameter of change over the course of treatment was significantly reduced in the verum group compared to all other groups (Kruskal-

Wallis chi^2 = 13.12; P = 0.004, Fig. 1 b) and especially compared to placebo (Mann-Whitney Z = –2.30; P = 0.021). No differences were detectable between the other groups. The treatment-baseline difference for the nocturnal portion of 24 h activity (delta P_n) showed a significant reduction of 16% in the verum group (Kruskal-Wallis chi^2 = 12.18; P = 0.007, vs placebo: Mann-Whitney Z = –2.50; P = 0.012), but not in the other groups.

To represent changes in clinical scales, we calculated the treatment-baseline proportion of the NPI total score and NPI agitation subscore (Table 2). For the NPI, we were unable to detect any differences between treatment conditions; however, the NPI agitation subscale showed a reduction for the verum group (Mann-Whitney Z = –2.13; P = 0.033).

There was no correlation between actigraphic and clinical scale values. No differences were detectable between clinical responders (defined as at least 50% reduction of NPI or NPI-agitation subscale) and non-responders for any actigraphic parameters.

The average number of additional medications per day during the trial was 0.76 units (SD = 0.81) for the verum group and 0.89 units (SD = 1.29) for the placebo group without significant difference between both groups.

Discussion

In this study, we present actigraphic parameters that represent the actual clinical status (cross-section) of patients, such as AA_n or $AA_{24,}$ and parameters that summarise changes over the course of time, such as AA_n ratio or delta P_n. We also calculated the corresponding values using the gold standard clinical scale (i.e. the NPI and its subscales).

In both healthy subjects and patients with BPSD there were large interindividual differences in actigraphic motor activity and thus a wide distribution of absolute values for activity measures. This is due to actual quantitative differences in individual basal motor activity and small technical deviations in the measuring instruments.

However, intraindividual actigraphic motor activity remains stable over time; as a result, any differences associated with a particular intervention should be easily detectable. This means that relative intraindividual changes over the course of treatment are the best parameters for actigraphic monitoring. In our data, AA_n and delta P_n are precisely such intraindividual parameters of change; these only showed significant differences in the verum group. Because of the large distribution of values, classifying an individual to the proband or patient group (e.g. for diagnostic reasons) is not possible. Interestingly, the activity levels of agitated demented patients appear to have been similar to those of healthy elderly subjects and were reduced in verum treated patients. Thus, disturbed behaviour in BPSD might be a qualitative, rather than a quantitative, issue with regard to motor activity. On the other hand, the main effect of pharmacological treatment might be a quantitative decrease in motor activity.

In our study of patients with BPSD, both actigraphic data and clinical scales detected differences between the placebo and verum groups. In particular, it was the cross-sectional parameters AA_n and NPI (under treatment conditions) and the parameters of change over the course of treatment (i.e. AA_n ratio, delta P_n, and the treatment-baseline ratio of NPI scores) that were able to distinguish between the two patient groups.

In contrast to our hypothesis, there was no positive correlation between the changes in motor activity detected by means of actigraphy and the changes measured using the NPI agitation subscale. It seems as if both methods monitor different aspects of BPSD, each of which reacts differently to therapy. It is impossible to determine whether actigraphic or NPI data more closely represent the clinically relevant symptoms. Additional parameters should be examined for global clinical outcome, such as time until long-term hospitalisation or care givers' quality of life.

Because research on BPSD is increasingly focusing on pharmacotherapy, a large number of methods are currently being discussed for monitoring clinical symptoms. In general, scales are subjective and dependent on personnel resources. In contrast, objective measures such as actigraphy have only been used rarely to date; not surprisingly, they have yet to be validated for this group of patients. Obtaining polysomnographic data would be the best way to examine night-time agitation, but this is not possible in the majority of AD patients. The ability of actigraphy to measure parameters such as sleep duration or sleep efficacy has been the subject of controversy [1]. So far there have been no studies comparing actigraphy with polysomnography in demented patients. As a result, we have refrained from calculating such parameters in the present investigation.

This study shows that intervention-related changes in motoric activity in demented patients can be detected using actigraphy. Actigraphy is an objective and easy-to-use tool for evaluating the course of treatment in patients who are difficult to examine by other means.

Conclusion

In pharmacotherapeutic research, in particular, many methods have been discussed to monitor behavioural and psychological symptoms of dementia (BPRS). In general, clinical scales are subjective and personnel-intensive. In our study, actigraphy – as a direct and objective measure of night-time agitation – was able to distinguish between verum and placebo groups, but did not correlate with clinical scales. This may mean that the motor activity measured by actigraphy represents a distinct aspect of BPSD.

Activity levels in agitated patients with dementia were similar to those seen in healthy elderly subjects and were reduced in the verum group. Because of this, it seems that disturbed behaviour is a qualitative rather than a quantitative problem in BPSD. On the other hand, the main effect of pharmacological treatment might be a quantitative reduction in motor activity.

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