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Morningness and eveningness: When do patients take their antiepileptic drugs?

Wytske A. Hofstra [a,b,*], Job van der Palen [c,d], Al W. de Weerd [a]

[a] Department of Clinical Neurophysiology and Sleep Center SEIN Zwolle, Netherlands
[b] Department of Neurology, Medisch Spectrum Twente Hospital, Enschede, Netherlands
[c] Medical School Twente, Medisch Spectrum Twente Hospital, Enschede, Netherlands
[d] Department of Research Methodology, Measurement and Data Analysis, University of Twente, Enschede, Netherlands

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ABSTRACT

Almost one-third of epilepsy patients continue to have seizures despite adequate drug treatment. Chronotherapy (based on dynamic changes in drug pharmacology and disease-related processes) could be a promising treatment option. We aimed to explore whether different circadian types adjust administration times of antiepileptic drugs (AEDs) as a step in exploring chronotherapeutic possibilities. We performed a questionnaire-based study to compare behavior of different circadian types in relation to times of taking drugs. Circadian type was determined by the Morningness–Eveningness Questionnaire. Results clearly show that morning types are taking their AEDs significantly earlier than do evening types on free days. Times of taking AEDs in the morning on work days also differ significantly between morning and evening types. Regardless of circadian type, drugs on free days are taken later than on working days. In conclusion, our study shows that patients adapt times of taking medication to their circadian type.

1. Introduction

Almost one-third of epilepsy patients continue to have seizures despite adequate drug treatment (antiepileptic drugs, AEDs) [1,2]. Besides the development of new drugs and other treatment options, it is also important to investigate how current AEDs can be used better to improve seizure control. Chronotherapy, which is delivery of therapy based on the dynamic changes in both drug pharmacology and disease-related processes [3], could be a new option.

Chronotherapy is already used in various diseases, such as cancer, pulmonary disease (e.g. allergic rhinitis and bronchial asthma), cardiovascular diseases, and in the treatment of pain [4–6]. Several studies have shown that administration of drugs adjusted to the circadian rhythm can be successful, not only in reducing symptoms, but also in reducing adverse drug effects and thereby improving quality of life [7]. Whether chronotherapy will be successful depends on several factors, i.e. the circadian differences in pharmacodynamics of the specific treatment and the 24-hour pattern in manifestation and intensity of symptoms in a disease. In epilepsy, various AEDs are being used with different pharmacodynamic profiles. Also, it has been shown in recent human studies that seizures may occur in different 24-hour patterns [8–12]. Therefore, there is good reason to believe that chronotherapy could improve seizure control. To our knowledge, only one group has investigated this option in epilepsy patients. Yegnanarayan et al. changed administration times in patients with diurnal seizures that were not controlled by phenytoin and/or carbamazepine [13]. The authors found that by adjusting administration times from 0800 h to 2000 h, therapeutic drug levels were achieved more easily and toxic manifestations were reduced. Until now, no other epilepsy studies have been published on adjusting therapy to a person's circadian type or chronotype, while large differences between individual chronotypes exist.

Before studying whether adjustment of medication administration times leads to improved seizure control, the spontaneous behavior of patients towards these times has to be studied. For instance, in our tertiary center, patients are prescribed with AEDs the advice to take these drugs at certain times. These times are 0800 h, 1200 h, 1800 h and 2300 h, depending on the frequency per day. However, it is conceivable that an extreme morning type who gets up at 0600 h in the morning tends to take the medication far before 0800 h, and someone that is used to getting up late will take the medication later than the advised time. Therefore, this study focuses on the moments that patients take medication in practice. We hypothesize that these times vary strongly between morning, intermediate and evening types.

2. Methods

2.1. Subjects

Patients from the nationwide epilepsy center SEIN were approached to complete a questionnaire to determine their circadian

* Corresponding author at: Medisch Spectrum Twente Hospital, Department of Neurology, Postbus 50000, 7500 KA Enschede, Netherlands. Fax: +31 53 4872882.
E-mail address: w.hofstra@mst.nl (W.A. Hofstra).

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type and to fill in the average times when they take their AEDs on work or school days and free days separately.

The study was approved by the institutional Medical Ethics Committee. Subjects were not paid for participation.

2.2. Assessment of circadian type

A validated questionnaire was used to determine the patients' circadian type. This questionnaire was the Morningness–Eveningness Questionnaire (MEQ). This was originally developed by Horne and Ostberg and differentiates morning, intermediate and evening types [14] and was validated for Dutch language by Kerkhof [15].

2.3. Data analysis

The MEQs were processed according to the manual, with possible scores ranging from 16 through 86 (with 16 expressing a definite evening type and 86 a definite morning type). The group was split into three groups according to MEQ scores: evening types (16–41), intermediate types (42–58) and morning types (59–86). Times of taking medication in the morning and evening on work or school days and free days were compared between the three groups. Furthermore, differences between taking AEDs on work days and free days were assessed. Gender and age differences were also determined.

To compare times of taking medication on work versus free days within the groups, paired *t*-tests were used, and to compare gender differences the unpaired *t*-test was applied. Differences in timing between the morning, intermediate and evening types were analyzed using the ANOVA test with Tukey's Honestly Significant Difference post hoc test. As in the AED group and in the group of evening dose on free days, the standard deviation was significantly different; the Welch's test was used. Because of the age differences between the groups, linear regression was also applied to correct for these age differences. Furthermore, effect modification by age (younger half of the group versus older half of the group) was assessed. Significance was set at p level of 0.05. For statistical analysis SPSS v17 (SPSS Inc., Chicago, Illinois, USA) was used.

3. Results

Two hundred and eight adult patients (97 M/111 F; mean and median age 37; range 15–64) were included in the study. All patients were using AEDs.

According to the MEQ scores, the group was divided into morning types (n = 67), intermediate types (n = 122) and evening types (n = 19). For further characteristics, see Table 1A.

3.1. Free days vs work or school days

Of our 208 subjects, 65 did not work or go to school and four subjects indicated they had one work or school day per week. Respectively nine subjects had two work or school days; 19 had three and 33 subjects worked or went to school for four days a week. 68 subjects did so for five days a week, and respectively seven and three subjects indicated they worked or went to school for six and seven days a week. For the distribution between morning, intermediate and evening types, see Table 1B.

Table 1A
Characteristics of the patient population.

	Morning types	Intermediate types	Evening types	
Age (median) in yrs	27.8 (27.0)	35.3 (32.0)	43.4 (44.5)	
Gender	27 M; 40 F	61 M; 61 F	9 M; 10 F	
Mean MEQ scores	64.3 (59–75)	51.4 (42–58)	37.3 (28–41)	
Mean MSF[a]	0314 h	0414 h	0540 h	
Total	67	122	19	208

[a] MSF: mid-sleep on free days corrected for sleep duration on work and free days.

Table 1B
Number of working/school days (%).

	Morning types	Intermediate types	Evening types
0	40	30	16
1–3	16	12	32
≥4	45	58	53

3.2. Antiepileptic drugs

Eighty three subjects were on monotherapy, 84 used two different AEDs and 41 used more than two different AEDs (34 used three, six patients used four and one patient used five different AEDs). Most frequently used AEDs in this population were valproic acid (39%), carbamazepine (36%) and lamotrigine (36%), followed by levetiracetam (22%). There was no difference in the number of AEDs taken by morning, intermediate or evening types. Nineteen patients took AEDs once a day, 122 patients took them two times a day, 46 were on a thrice-a-day schedule and 21 patients were on a four-times-a-day schedule. As most patients were taking medication in the morning (prescribed on 0800 h, n = 188) and early evening (prescribed on 1800 h, n = 161), these data were analyzed.

3.3. Differences between morning, intermediate and evening types

In the morning type group, the average times of taking medication in the morning on work or school days was 14 min ($p = 0.006$) earlier than in the intermediate group and 55 min earlier than in the evening type group ($p < 0.001$). The times of taking evening medication did not differ between morning, intermediate and evening types on work days (see Table 2 and Fig. 1).

Significant differences were seen in times of taking medication in the morning when the individual was free. Morning types took their AEDs 45 min earlier than the intermediate types ($p = 0.004$) and 100 min earlier than the evening types ($p < 0.001$). Times for the evening dosage only differed between morning and evening types (55 min, $p = 0.019$, see Table 2 and Fig. 1).

3.4. Differences between work days and free days

In the morning group, patients delayed taking their morning medication on free days by 41 min ($p < 0.001$), the intermediate types took their medication 76 min later ($p < 0.001$), while the evening types delayed their morning dose by 90 min ($p = 0.005$) in comparison to work days (see Fig. 2). In the evening, taking medication was also later on free days than on working days in the intermediate group (15 min, $p < 0.001$), but not in the morning and evening groups.

In the 208 subjects, regardless of morningness or eveningness, administration times in the morning were on average 68 min later on free days than on work days (0742 h vs 0850 h, $p < 0.001$). Times for the evening dosages also differed (1811 h vs 1826 h, $p < 0.001$).

Table 2
Mean times of taking antiepileptic drugs (in hours).

	Morning types	Intermediate types	Evening types
Working days	0729 [0600–0900]	0743 [0545–1030]	0824 [0730–1000]
	1800 [1400–2150]	1814 [1600–2100]	1832 [1700–2000]
Free days	0814 [0700–1100]	0859 [0630–1300]	0954 [0800–1300]
	1807 [1600–2130]	1829 [1615–2300]	1902 [1700–2200]

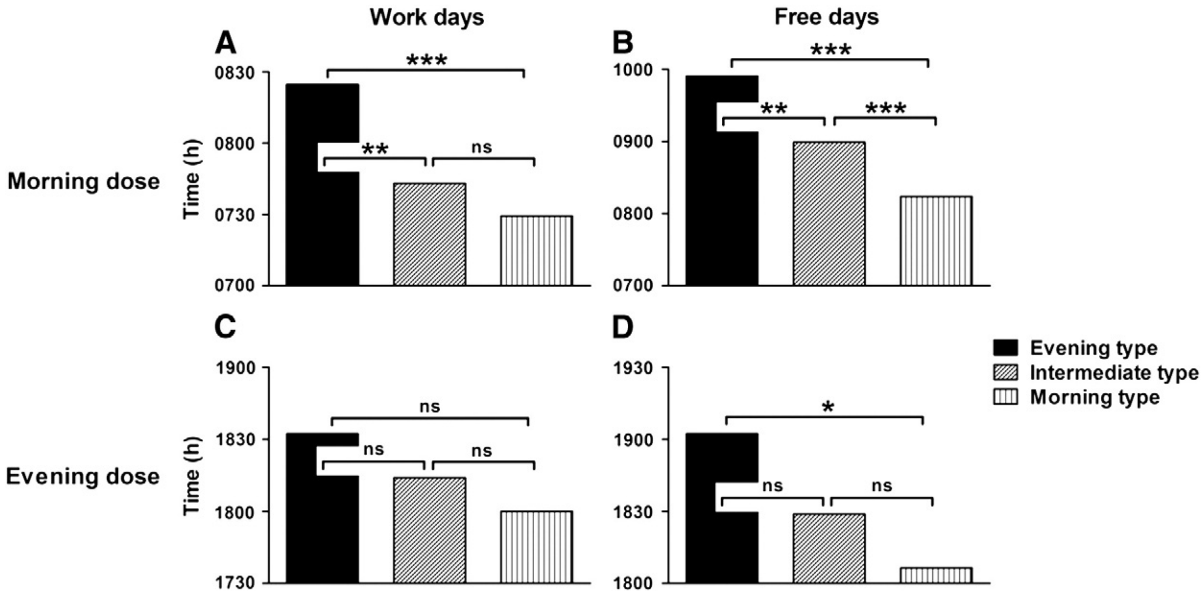

Fig. 1. Bar graph showing the mean timing of drug administration in different circadian types in the morning on work days (A) and free days (B). Timing of evening dose is shown in C (work days) and D (free days).

No differences were seen when comparing the administration times of female and male patients. Also, there was no effect modification by age in the relationship between chronotype and the time the AEDs were taken.

4. Discussion

The main finding of this study is that epilepsy patients adapt their drug administration times to their circadian type. On free days, morning types take their AEDs significantly earlier than do evening types, with most pronounced differences in the morning doses. Also, times of taking AEDs in the morning on work days differ between morning and evening types. Furthermore, in general, drug administration times are significantly delayed on free days compared to work days.

Many epilepsy patients continue to have seizures with the current drugs. Among others, chronotherapy may offer a solution to drug-resistant epilepsy. Although chronotherapy is being used in various other disorders, it is not (yet) being applied in epilepsy. However, before chronotherapeutic options in epilepsy can be explored, one needs to know at what times drugs are used by patients in practice. To our knowledge, this is the first study focusing on the influence of circadian typology in drug administration times. We have included a large group of morning, intermediate and evening types to see whether patients adapt these administration types to their biological

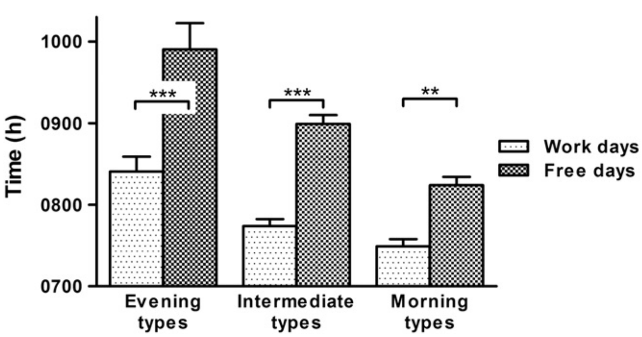

Fig. 2. Bar graph showing the difference in mean timing of drug administration in the morning, comparing work and free days in the evening, intermediate and morning types. Data are expressed as mean ± standard error of the mean.

preferences in daily activities and sleep–wake cycle. By means of a widely used and validated questionnaire, we have assessed the individual's circadian type and correlated this to the individuals' drug administration times.

There are limits to this study. One has to realize that filling in the times of taking medication is subjective. Patients might not be completely honest, and might fill in what they think is appropriate. This would mean that in reality administration times would vary even more. Also, we asked the patients to fill in the average times of taking medication, therefore we might miss intraindividual variation. Besides that, patients might have help of, for instance parents and spouses, when taking medication, which might influence times of taking medication. We have not included that question in our questionnaire. Furthermore, our evening type group is rather small in comparison to the two other groups. Finally, in this study, we have not correlated seizure occurrence to times of taking AED. Due to the heterogeneity of epilepsy syndromes and due to the subjective measure (the use of questionnaires), a true reflection of seizure control cannot be given. For instance, a person with nocturnal frontal lobe epilepsy will not be able to truly indicate a number of seizures. This shortcoming of the current study needs to be addressed in further studies by EEG and video registration.

As results of this study show that patients take their AEDs adapted to their level of morningness/eveningness, physicians need to realize this when prescribing drugs to their patients. In itself, this adaptation to the circadian type does not pose a risk. However, if drug administration times on free days are significantly delayed compared to work days, like in evening types on average by 90 min, this irregularity could contribute to poor seizure control. Therefore, in case of poor seizure control, it may be helpful to ask patients to fill in their drug administration times on work days and free days, as we have done in this study, to discover such irregularities. Furthermore, it would be valuable to emphasize the importance of taking drugs at the same time every day, regardless of whether it is a free day or a work day.

Modern day society is build around morning and intermediate types. Schools start in the early morning and the same goes for most jobs. Therefore, many people have to adapt their sleep–wake cycle to the society. As intermediate and evening types go to bed later than do morning types, but still have to rise early, they often sleep too little during the week. This can lead to a sleep debt, the cumulative effect of not getting enough sleep, built up during the week. Therefore, it makes sense that intermediate and evening types get up later on free days than on work days for two reasons. First, because of their biological clock and second, because of catching up with lost sleep. This, in turn, causes the larger differences between taking morning medication on work days and free days in comparison to morning types.

Taken together, there are two kinds of imposed schedules of timing of taking medication. First, the schedule proposed by the physician and second, the imposed schedule created by demands of modern day society. Both may lead to irregularity in times of taking medication, especially in evening types, as the imposed schedules fit morning types best. Irregularity in times of taking medication might lead to diminished seizure control, which is important to realize when evaluating drug treatment in epilepsy.

In conclusion, we have shown that there is morningness/eveningness in the times at which patients take their medication, which means that patients adapt these times to their circadian type. Also, results show that patients delay times of taking medication on free days significantly compared to work days. Further research is needed to see whether these findings are confirmed when circadian rhythmicity is measured in epilepsy patients by, for example, the melatonin curve or core body temperature [16]. Furthermore, correlation of seizure occurrence and seizure severity to timing of AEDs in different circadian types can show whether adaptation of drugs to the individual circadian rhythm might improve seizure control. A step further would be to consistently adjust the drug administration times to the patient's circadian or chronotype to see whether this decreases seizure frequency, severity and adverse effects.

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