ANNUAL REVIEW OF CHRONOPHARMACOLOGY

Volume 1

BIOLOGICAL RHYTHMS AND MEDICATIONS

Proceedings of the First Montreux Conference of Chronopharmacology, Montreux, 26–30 March 1984

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CIRCADIAN DYSRHYTHMIA IN THE BEHAVIOR OF EPILEPTIC CHILDREN WITH CLONAZEPAM AND/OR PHENOBARBITAL TREATMENT

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ABSTRACT

To evaluate the influence of anticonvulsants (clonazepam and phenobarbital) on behavior rhythms of children, fifteen 24-hr-observations with 1 observation unit per minute of the behavior of 3 healthy children without treatment and 12 epileptic children with phenobarbital and/or clonazepam treatment were performed on standardized hospital terms for several behavior parameters. The results demonstrate that clonazepam might cause grave circadian dysrhythmias, whereas phenobarbital does not alter circadian behavior rhythms to the same extent.

KEYWORDS

Petit mal epilepsy, children, behavior, clonazepam, phenobarbital, circadian dysrhythmia.

INTRODUCTION

In clinical practice, alterations of the sleep-waking cycle (drowsiness) or of other behavior components are quite often observed side effects of anticonvulsive medication. Nevertheless, some authors (Chemburkar, 1976) suggested that anticonvulsive effects of these drugs should be considered isolatedly from sedative side effects, the side effects disappearing after a while of drug administration. Therefore, the present study is an attempt to quantify the often fatal side effects in the behavior of long-term treated epileptic children by systematic clinical 24-hr observations.

METHODS

Subjects: Three groups of children with infantile spasms (a petit mal epilepsy) were studied. All epileptic children received anticonvulsivants in non-toxic plasmatic ranges. The first group C consisted of 3 patients who were treated by clonazepam only (mean age $\pm$ S.E.M. 14 $\pm$ 4.6 months, 2 female (f) 1 male (m)), the second group PC consisted of 6 patients who

got a combination of phenobarbital and clonazepam (mean age of 13.3 ± 1.8 months, 4 f, 2 m) and the third group P consisted of 3 children who received phenobarbital only (mean age of 14.7 ± 6.1 months, 1 f, 2 m). A control group (Co) of 3 healthy subjects did not receive any treatment.

Procedures: All children were observed with observation unites of 1 min. by a trained team of four persons on standardized hospital terms within a 24-hr time span for 30 behavior parameters defined precisely beforehand. Only seven parameters (with highest incidence) were analysed by statistical methods: Incidence of sleep, restlessness, ocular seizures, epileptic seizures, weeping/crying, singing or similar sounds, arm movements. Nearly all children got medication regularly every 8 hrs (at 0700, 1500, 2200), and there was no difference to be found in children with irregular and regular medication scheme, whose results were therefore combined. Food intake hours (at 0700-0730, 1130-1200, 1600-1630) were also taken into account, but don't seem to influence the results. Plasmatic drug levels were controlled at 10.00 a. m. on the first day of the 24-hr observation. A continuous plasma drug level monitoring was impossible for technical and ethical reasons.

Analyses and calculations: Hourly data were analysed by the single cosinor method with trial periods (τ) = 24, 12, 8, 6 and 4 hrs for each parameter, each patient and each group. Basing on these results, the rhythm detection rate was calculated for the respective groups and periods by dividing the number (n) of rhythm detections to be found by the cosinor (with $p < 0.05$) by the total of the theoretically possible detections (all investigated parameters (i) · members of the group (m)):

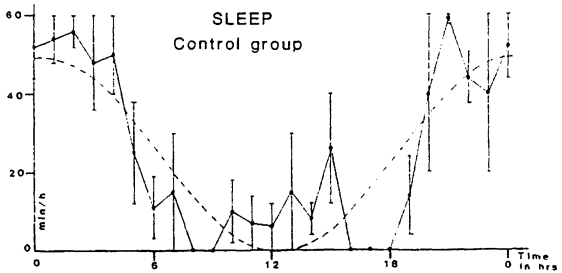
$$\frac{n}{i \cdot m}$$

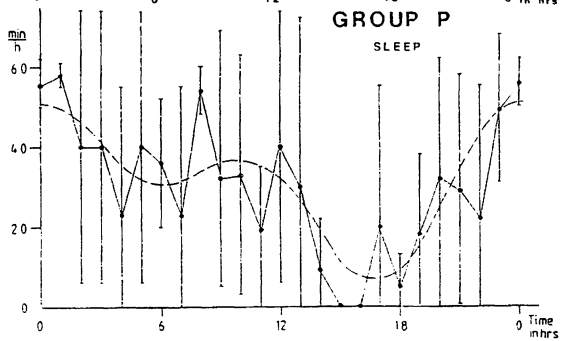
The rhythm detection values (in %) were compared by the χ^2-test for evaluating a statistically significant difference among the four groups.

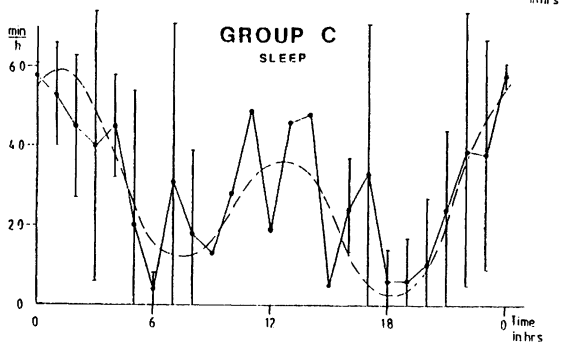
RESULTS

Figures 1 - 4 show the raw data and best fitting cosinor curve for the sleep incidence of the 3 treated groups and the control group. The control group shows a higher amplitude than all groups with anticonvulsive treatment and only a circadian sleep rhythm, whereas the groups C, PC and P exhibit ultradian sleep rhythms of which the 8-hr period in the group PC has to be considered as anormal in this age (Hellbrügge, 1964). Concerning the amplitude, no larger difference can be seen among the single treatment groups.

In figure 5 the rhythm detection rate resumes the results in an instructive manner: While phenobarbital results are hardly different from the control group, the groups PC and C (with combined or single clonazepam treatment) show that the circadian component of the behavior (7 parameters!) has mostly (PC) or totally (C) disappeared and that pathological 8-hr rhythms are persisting despite of the age of more than 1 year (group PC) or have even become predominant (group C). It is also impressively demonstrated (control group) that ultradian rhythms should normally have been disappeared in this age







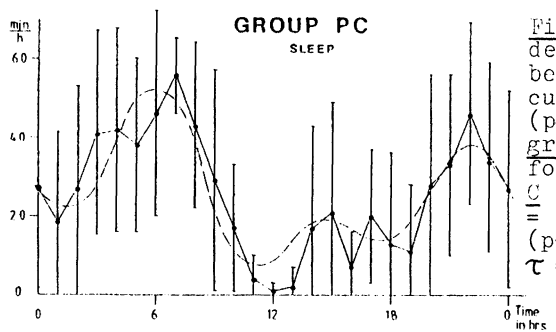
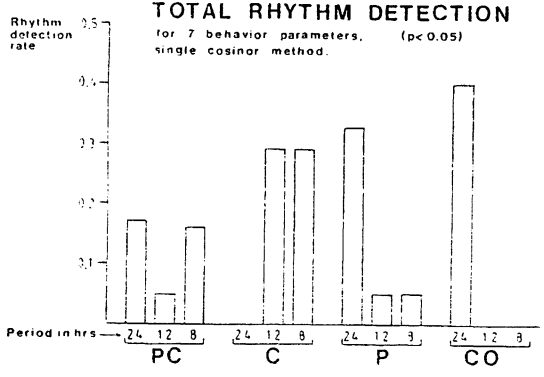


Fig. 1-4. Sleep incidence. Raw data and best fitting cosinor curves. Control group ($p<0.000$ for τ = 24 h), group P ($p<0.01/0.05$ for τ = 24/12 h), group C ($p<0.05/0.000$ for τ = = 24/12 h), group PC ($p<0.000/0.05/0.01$ for τ = 24/12/8 h).

Fig. 5. Rhythm detection rate in %.

χ^2-test:

period (τ)	d. f.	p
24 (h)	3	< .1
12 (h)	3	< .025
8 (h)	3	< .1



range (with the exception of small 12-hr rudiments to admit).

DISCUSSION

Previous studies by Hellbrügge (1963, 1974), Parmelee (1961) and others showed that physiological and behavioral parameters gradually become circadian rhythmic after a few days (electric skin resistance in the first week, Hellbrügge 1963). Thus, the sleep-waking cycle normally gets a circadian organisation at the age of 1 - 7 months.

In this study we found circadian dysrhythmias in children with infantile spasms treated by anticonvulsants which could be due to 1. the epileptic disease or the often associated cerebral disorder, or 2. the anticonvulsive medication. The first hypothesis cannot totally be rejected, but does not seem probable because of the differences we found among the phenobarbital and the clonazepam groups. Therefore we suggest that clonazepam is is able to cause grave circadian dysrhythmias and anormal 8-hr rhythms in the behavior of children. Phenobarbital, however, seems to be an anticonvulsive drug which does not influence circadian rhythms of the behavior and the sleep-waking cycle.

Further studies with a larger number of patients are suggested to establish a reasonable chronotherapy with anticonvulsive drugs and above all clonazepam. In this way, the fatal side effects which often augment the social and mental isolation of these patients already handicapped by their disease, could be diminished (together with an eventually augmented efficacy of anticonvulsants).

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