Melatonin does not Influence Sleep Deprivation Electroencephalogram Recordings in Children

Julia Sander, Mohammed Ghiath Shamdeen, Sven Gottschling, Ludwig Gortner, Stefan Gräber and Sascha Meyer

Abstract
The electroencephalogram (EEG) is an essential diagnostic tool in children with epilepsy. The recording of a sleep EEG can increase the yield of EEG recordings in certain epileptic syndromes. The primary aim of this study was to assess the influence of melatonin on EEG recording (quality, EEG characteristics) and to assess its efficacy to induce sleep. Children with epilepsy or non-epileptic neurological patients requiring sleep deprivation EEG studies were enrolled into this prospective study at a tertiary University Hospital study. Sequential recording of sleep deprivation EEGs both with and without prior administration of melatonin was performed. A total of 50 patients (27 with epilepsy, 23 non-epileptic neurological patients) were included in this study (median age 9.5 years; range 1–18 years; male 28). The quality and EEG characteristics (abnormal findings, depth of sleep) were not affected by the use of melatonin. In total, 92 of 100 EEGs were successfully performed without significant differences between the two groups (six failures with melatonin, two failures without melatonin; p = 0.289).

Conclusions: We conclude that melatonin does not alter the quality of sleep EEG studies in children with epilepsy or suspected epilepsy. Melatonin does not increase the rate of successfully performed EEG studies in sleep-deprived children.

Introduction
In order to properly perform diagnostic procedures in children, adequate patient cooperation is needed. The recording of an electroencephalogram (EEG) is often not well tolerated by children, especially in children with developmental disabilities. Neuropsychologic investigations in children, particularly in the earlier stages of life, are often recorded during sleep. In small children, this can increase the amount of information on maturation of brain electrical activity and reduces the occurrence of artifacts due to inadequate cooperation. Moreover, sleep can also increase the yield of the test itself, as for the EEG in certain epileptic syndromes, and this seems particularly true for EEG recordings after sleep deprivation.

Sleep in children is usually achieved either by partial deprivation or by the administration of sleep-inducing drugs (sedatives). The realization of sleep deprivation is burdensome for both the patient and the family. Pharmacological agents including barbiturates, chlorpromazine, and chloral hydrate are used to induce sleep, and most of them can influence sleep macrostructure and/or affect the interpretation of the recorded EEG data.

The sleep inducing effect of melatonin, a hormone secreted by the pineal gland, has been reported in adults, animal research, and children. Moreover, melatonin has been recommended for use in children with epilepsy since it has been shown to improve the quantity and quality of sleep, thus reducing the probability of sleep deprivation induced seizures in these patients. Animal research has demonstrated that melatonin suppresses epileptic discharges.

While recent reports have shown that melatonin can reliably induce sleep in children, only very little data are available with regard to the clinically important question whether melatonin influences EEG recordings in children. Therefore, the primary aim of this study was to determine whether melatonin affects or alters the quality and characteristics of EEG recordings in children both with epilepsy and other neurological problems.

Methods
This study was done in accordance with the policy of the Institutional Review Board and after approval by the Ethics Committee of the University Hospital of Saarland, Saarbrücken, Germany. In all patients, parental consent was obtained prior to enrolment.

Enrolment Criteria
Patients (aged 1-18 years) were admitted to our hospital with a history of epilepsy or developmental delay/neurological problems that required the recording of a sleep deprivation EEG for diagnostic work-up according to our hospital policy.

EEG Recordings
A 19-channel EEG recording was performed using a standardized approach. Twenty silver cup electrodes were placed according to the 10–20 international system. Electrode impedances measured less than 5 kΩ. An IT med® (IT Medical, Usingen, Germany) model EEG Neurofile NT/XP machine was used. A high-frequency filter was set at 70 Hz; bipolar longitudinal and transversal montages were used. Each EEG recording lasted 25–30 min. EEG recordings were evaluated by two experienced neuropediatricians (SM and MGS), based on conventional EEG criteria. Age-dependent EEG differences were taken into account. Sleep stages were defined according to the proposal by Rechtschaffen and Kales.
In all children, we performed a sleep deprivation EEG study. For this purpose, children went to sleep between 07:00 and 09:00 p.m. and were woken up between 2:00 and 03:00 a.m. and were kept awake (parents were asked to keep their children actively entertained during the night) until the recording of an EEG was performed at around 07:30 a.m. To avoid falling asleep during the trip by car to our hospital, a second adult person was accompanying the child. The recording of the EEG study lasted 25-30 min. At the end of the EEG recording, children were gently woken up by the EEG technician. In addition to the sleep deprivation EEG study, a second EEG was performed. For this second EEG study, children were woken up in a similar manner, and additionally, melatonin was given (in children ≤7 years, 5 mg; children >7 years, 10 mg of fast-liberation) liquid melatonin (dissolved powder) when presenting to our outpatient clinic, approximately 15–20 min prior to proceeding to the EEG lounge and positioning of the EEG probes. The start of the EEG recording commenced approximately 30–40 min after melatonin administration. To avoid cross-over effects, the order of the two EEG recordings (with and without melatonin) was random. Only children who did not experience changes in their antiepileptic drugs (AED) medication during that time interval were included in the trial.

The following data were collected: baseline characteristics (patient’s age, type of epilepsy, AED medication, time interval between the recordings, etc.). Furthermore, we assessed exact duration of sleep deprivation, induction time (time until sleep onset (both clinically as demonstrated by video recording and stage 1 of sleep)), EEG quality, patient artifacts (movement, muscle, unwanted arousal, etc.), depth of sleep in EEG, and abnormal findings on EEG (occurrence of epileptic potentials). The quality of the EEG (i.e., the occurrence and amount of artifacts) was graded on a scale from 1 to 5 (1 = no artifacts; 2 = some, minor artifacts; 3 = moderate amount of artifacts; 4 = substantial amount of artifacts, but EEG recordings could be assessed; 5 = unsatisfactory/invalid; EEG could not be assessed), similar to the Likert assessment scale.

**Statistical Analysis**

The data are presented as medians and ranges, and frequencies. To compare normally distributed quantitative data, we used Student t test, otherwise the Mann-Whitney U test. For comparison of qualitative variables, we employed the McNemar test. A p value<0.05 was considered significant. SPSS statistical program was used for data storage and analysis (SPSS. 19.0, Chicago, IL, USA).

### Results

Between September 2009 and August 2011, 50 children were enrolled in this study, and a total of 100 EEGs were recorded. Patients’ demographics are detailed in Table 1. In 21 children, the initial EEG recording was done after sleep deprivation and additional melatonin administration; in the remaining 29 children, the first EEG recording was done following sleep deprivation only. The subsequent EEG recordings were done the other way around.

The median time interval between the recordings was 35 days (range 10-68 days) for the epilepsy group and 23 days (range 8–45 days) for the non-epilepsy group (for all patients: median 26; range 8–68 days); difference between epilepsy and non-epilepsy group; p* = 0.024). The median time of sleep deprivation was 360 min (range 270–490 min) in the melatonin group and 330 min (range 278–483 min) in the non-melatonin group (p = 0.664). Thirty-six children received 10 mg melatonin while 14 children were given 5 mg prior to the EEG recording.

Successful sleep onset (induction time after starting EEG recordings) occurred after a median time of 5 min in both the melatonin group (range 2–7 min) and in the non-melatonin group (range 3–7 min) (p = 0.544). The quality of the EEG recordings was comparable with melatonin although somewhat more artifacts were seen in the melatonin group (artifacts 26 of 50) and without melatonin (artifacts 16 of 50; difference between melatonin and non-melatonin group; p = 0.064).

The depth of sleep in both with and without melatonin is depicted in Table 2. The number of unsuccessful EEG recordings because of failure to induce sleep was higher in the melatonin group (6 vs. 2; p = 0.289). The time interval of sleep deprivation was similar in children with failure (in the melatonin group). No episodes of premature arousals were seen in any patient.

Abnormal findings (epileptic discharges, focal or generalized slowing) were evenly distributed, irrespective of the use of melatonin (20 of 50 in both groups). No side effects occurred in the melatonin group. In particular, administration of melatonin was easy to handle and was well tolerated by all patients (e.g., no episodes of vexing, etc.).

### Discussion

Sleep is a physiological state during which vigilant consciousness is temporarily abolished and responses to environment stimuli are decreased. It is cyclic and associated with various changes in behavior, endocrinal, and other physiological functions. Epilepsy is a state of recurrent unprovoked seizures. The existence of relationship between sleep and epilepsy has long been observed but was first validated by Gibbs and Gibbs.
Table 2. Stages of Sleep Depending on Whether Melatonin was Given or Not

<table>
<thead>
<tr>
<th>Depth of Sleep</th>
<th>Melatonin Group</th>
<th>Non-Melatonin Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not asleep</td>
<td>6 (failure)</td>
<td>2 (failure)</td>
</tr>
<tr>
<td>Stage 1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Stage 2</td>
<td>24</td>
<td>29</td>
</tr>
<tr>
<td>Stage 3</td>
<td>13</td>
<td>11</td>
</tr>
<tr>
<td>Stage 4</td>
<td>7</td>
<td>8</td>
</tr>
</tbody>
</table>

When they found that paroxysmal discharges occurred more frequently in sleep,3 Therefore, often a sleep-(deprivation) EEG is performed to elicit EEG abnormalities, although the number needed to test with sleep-deprived EEG to identify one additional child with epileptiform discharges is approximately 11.3

Lately, the use of melatonin has become increasingly popular to facilitate induction of sleep in both children and adults.3,4,5,6,7,8,9,10,11 Melatonin (5-methoxy-N-acetyltryptamine) is a pineal hormone; its synthesis is controlled by external factors including environmental light. Melatonin regulates sleep-wake cycles through its action on the suprachiasmatic nucleus in the hypothalamus. It has been widely used in the treatment of sleep-wake cycle disorders and showed great promise in the treatment of jet lag and other sleep disturbances. The major side effect of melatonin is drowsiness.

In this prospective study, we demonstrated that the use of melatonin does not alter the quality and characteristics of sleep deprivation EEG recordings in children. Melatonin was well tolerated in children with epilepsy and in children with other neurological problems without the occurrence of adverse effects. To our surprise, melatonin did not add a benefit with regard to increasing the number of children with successful induction of sleep. Of importance, no side effects were seen following the use of melatonin. However, in our series, in contrast a previous report,4 once children were asleep, no significant episodes of arousal were noted. However, it is important to note that the overall number of children included in this prospective trial was small. Moreover, we included heterogeneous study populations (both non-epileptic children with a variety of medical conditions and children with various types of epilepsy). Therefore, it will be important to conduct further, larger clinical trials with more homogeneous study populations on this issue before our data can be generalized for children with epilepsy.

To minimize or avoid cross-over effects between the two recordings, the order of the sequential recordings was chosen to be random. However, some differences between the two groups were seen (in 21 children initial EEG recordings were done without melatonin, in 29 children with melatonin), possibly influencing the results to some degree.

In a recent study, Ashrafi et al. demonstrated that detection of seizure activities in EEG was significantly higher in melatonin-induced sleep recordings compared to chloral hydrate.1 This is somewhat in contrast to our findings where abnormal EEG findings were identical between the melatonin and non-melatonin group. Conversely, Rowan et al. demonstrated in a previous study that sleep deprivation EEG recordings yielded a significant higher number of EEG abnormalities when compared to EEG recordings induced by various sedatives.14

However, the direct comparison between these studies is impeded by the fact that we did not compare melatonin to another sedative, sleep-inducing agent. Moreover, in our trial, melatonin was given in addition to partial sleep deprivation in order to evaluate its possible modifying effects on the EEG recording. The concurrent effects of sleep deprivation are also likely to be attributable to the short induction times seen in our study cohort, when compared to longer sleep onset latencies reported in a previous study (median 45 min).1

We conclude that melatonin does not influence the quality or characteristics of sleep deprivation EEG recordings in children, and it does not affect the occurrence of significant abnormal findings. Melatonin appears a safe medication in this patient cohort. However, melatonin failed to increase the number of patients with successful sleep induction, and a larger proportion of EEG recordings were unsuccessful, although these differences did not statistically reach the level of confidence. This may in part be attributed to shorter sleep deprivation times in the melatonin group, although these differences were statistically not significant.

Acknowledgments

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References


