Official Journal of the European Paediatric Neurology Society

Original article

Melatonin versus chloral hydrate for recording sleep EEG

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ARTICLE INFO

Article history:
Received 31 December 2008
Received in revised form
10 June 2009
Accepted 11 June 2009

Keywords:
Melatonin
Chloral hydrate
Sleep
Electroencephalogram

ABSTRACT

Although behavioral training could be successful in promoting electroencephalogram (EEG) compliance without restraint or sedation, sleep EEG may increase the yield of seizure activity. Furthermore uncooperative children not amenable to behavioral training require sedation for EEG recording. Our aim was to assess the impact of melatonin on the sleep EEG recording in comparison with chloral hydrate. Three hundred and forty eight patients (aged 1 month to 6 years) that were uncooperative with the EEG setup or referred for sleep EEG were enrolled in the study. Patients, partially sleep-deprived the night before, were randomly divided in two groups of melatonin and chloral hydrate on an alternative day basis, 174 patients in each group. Sleep onset latency in the chloral hydrate and melatonin groups was similar (Mann–Whitney test, $P = 0.113$). However, sleep duration and drowsiness time were significantly shorter in the group of melatonin compared to the group of chloral hydrate (Mann–Whitney test, $P < 0.0001$ and $P < 0.0001$ respectively). More patients in the melatonin group (20 versus six patients in the chloral hydrate group) required a second dose of sedative for sleep induction (chi square test, P value $= 0.004$). Seizure activities appeared in the electroencephalograms of 53% and 46% of patients in the melatonin and chloral hydrate groups respectively that were significantly higher in the melatonin group (chi square test, $P = 0.005$). Few adverse effects occurred in both groups (Fisher's exact test, $P = 0.64$).

The shorter sleep duration and drowsiness period were the two advantages of melatonin over chloral hydrate. Furthermore higher yield of seizure activity detection in melatonin sedated patients was in favor of its prescription for sleep EEG recording in the pediatric population.

1. Introduction

Performance of diagnostic medical procedures needs patient's cooperation that is often refused by children. The EEG procedure is especially not well tolerated by children with developmental disabilities. Although it has been shown that behavioral training is successful in promoting EEG compliance without sedation,[1] EEG recording in children not amenable to behavioral training often requires sedation. Furthermore natural sleep and sleep deprivation increase the yield of EEGs

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1090-3798/$ – see front matter
doi:10.1016/j.ejpn.2009.06.010

in detecting epileptiform abnormalities.[2,3] Sedation with chloral hydrate in addition to sleep deprivation is used to obtain sleep EEG recording in our institute.

Chloral hydrate is an organic halide that was first synthesized by Justin Liebig in 1832 and has been used as a hypnotic and sedative agent since 1869.[4–6] Its principle active metabolite, trichloroethanol (TCE) was discovered in 1948 by Butler.[4] Trichloroacetic acid (TCA) is another metabolite of chloral hydrate. Chloral hydrate likely exerts its effect on the central nervous system through TCE[4] with an unknown mechanism. Chloral hydrate is still used as a sedative agent prior to EEG procedures. However its unpleasant taste and side effects such as nausea, vomiting, ataxia, agitation, prolonged sedation,[6,7] delayed apnea events,[8] gastric irritation, potential carcinogenicity and genotoxicity[4] even as a single low dose[9,10] may warrant an alternative sedative for uncooperative children. Furthermore chloral hydrate is contraindicated in cases of peptic ulcers, hepatic insufficiency, porphyria, respiratory insufficiency, anticoagulant ingestion and hypersensitivity.[4]

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.[11] 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.[12] The major side effect of melatonin is drowsiness and it should not be prescribed in patients with leukemia, allergies, autoimmune diseases and severe mental disorders.

Melatonin has been used for sleep EEGs in adults[13] and children.[2] However to the best of our knowledge there is no study that compares melatonin with chloral hydrate for recording sleep EEG. Therefore our study was conducted to compare the sedative effects of these drugs and their impacts on the sleep EEGs.

2. Materials and methods

During the study period (September 2007–August 2008), all patients aged 1–72 months that were uncooperative with the EEG setup or referred to our electrodiagnostic department for sleep EEG recording were enrolled. Parents were asked to put their children to sleep 2 h later than the usual time, awaken them at 6.00 am and not to let them fall asleep until the time of EEG recording. Patients were randomly divided in two groups of melatonin and chloral hydrate for sedation. Informed consent was obtained from the patients' parents. Patients were excluded if they had hypersensitivity to chloral hydrate or melatonin, hepatic or renal impairment, severe cardiac disease, peptic ulcer, severe tonsillar or adenoid hypertrophy or were being treated with medications that have critical interactions with chloral hydrate or melatonin.

Chloral hydrate 5% one milliliter per kilogram of body weight and melatonin 2–6 mg were given orally 0.5–1 h before EEG performance. Regarding the pharmacodynamics of chloral hydrate and melatonin, EEGs were recorded 0.5–1 h after the sedative administration immediately when the child fell asleep to provide a similar condition for both groups. Melatonin liquid was supplied by NuPharm Laboratories Ltd, England and chloral hydrate was provided by Merck Company. Data were collected from a questionnaire filled out by trained EEG technicians. Collected data included neurological diagnosis, sleep onset latency, sleep duration, drowsiness time and adverse drug events that happened in the first 24 h after EEG performance. An analogue EEG machine (Nihon Kohden) was used with 21 scalp positions and the International 10-20 system. Electroencephalograms were interpreted by two pediatric neurologists. Statistical analysis was performed with SPSS/PC software (version 15). To compare qualitative data, chi square (χ^2) test and Fisher's exact test were performed. Non-parametric Mann–Whitney (M-W) test was used for comparison of non-normally distributed values between the two groups. A P value less than 0.05 was considered to indicate statistical significance. This study was approved by the ethics committee of the Tehran University of Medical Sciences.

3. Results

A total of 348 patients (male to female ratio of 1.3:1) were enrolled, 174 patients in each group of chloral hydrate (1–72 months of age) and melatonin (2–64 months of age). Referral reasons in the chloral hydrate group were seizure disorders in 131 patients (75%), developmental delay in 10 (6%), complicated breath-holding attacks in 17 (10%) and other causes in 16 patients (9%). Referral reasons in the melatonin group were seizure disorders in 127 (73%), developmental delay in six (3%), complicated breath-holding attacks in 17 (10%) and other causes in 24 patients (14%). Referral etiology was not significantly different between the two groups ($\chi^2 = 2.66$, df = 3, P value = 0.44). Sleep onset latency was between 10 and 150 min (median of 35 min) in the chloral hydrate group and 5–210 min (median of 45 min) in the melatonin group. Using Mann–Whitney test the sleep onset latency was not significantly different between the two groups (M-W = 13,656.5, $P = 0.113$). Sleep duration was between 15 and 240 min in both groups with a median of 60 and 30 min in the chloral hydrate and melatonin groups respectively. Sleep duration was significantly longer in the chloral hydrate group (M-W = 7871.0, $P < 0.0001$) (Fig. 1). Drowsiness time lasted 0–300 min in both

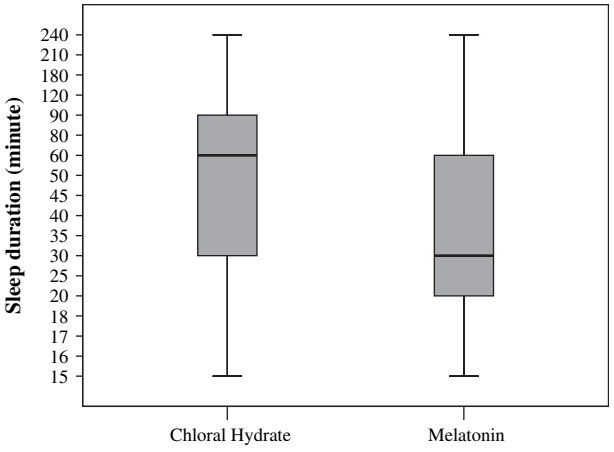

Fig. 1 – Box plot showing the median of sleep duration in groups sedated with chloral hydrate and melatonin.

Table 1 – Mann–Whitney test (M-W test) for the comparison of sleep characteristics between groups of melatonin and chloral hydrate.

Sleep onset latency[a]		P value (M-W test)	Sleep duration[a]		P value (M-W test)	Drowsiness time[a]		P value (M-W test)
Chloral hydrate range (median)	Melatonin range (median)		Chloral hydrate range (median)	Melatonin range (median)		Chloral hydrate range (median)	Melatonin range (median)	
10–150 (35)	5–210 (45)	0.113	15–240 (60)	15–240 (30)	0.0001	0–300 (60)	0–300 (20)	0.0001

a Values are expressed in minutes.

groups with a median of 60 and 20 min in the chloral hydrate and melatonin groups respectively that was significantly longer with chloral hydrate (M-W = 5707, $P < 0.0001$) (Table 1). A second dose of sedative was given to 26 patients (20 patients in melatonin versus six patients in the chloral hydrate group, $\chi^2 = 8.147$, df = 1, P value = 0.004) who had less than 15 min sleep duration that was inadequate for performing a thorough EEG. In this subgroup of patients, the sleep onset latency, sleep duration and drowsiness time of the second dose were considered for analysis.

Few adverse drug effects occurred in both groups (Fisher's exact test, $P = 0.64$). Diarrhea (two patients) and agitation (two patients) were the melatonin side effects. In the chloral hydrate group two patients had dizziness and another two patients had ataxia. Normal EEGs were found among 88 patients of the chloral hydrate group (51%) and 64 patients of the melatonin group (37%). Abnormal EEGs with epileptiform discharges were reported in 80 cases of the chloral hydrate group (46%) and 92 cases of the melatonin group (53%). The increased fast activity and slow dysrrhythmia in the EEG of 24 patients of our cohort were interpreted as drug effects on the electroencephalogram. Six patients sedated with chloral hydrate (3%) showed increased fast activities and 18 patients in the melatonin group (10%) had slow dysrrhythmia. Otherwise their EEGs were normal (Fig. 2). Chi square test showed higher detection of seizure activities in patients sedated with melatonin ($\chi^2 = 10.6$, df = 2, $P = 0.005$).

4. Discussion

Chloral hydrate is a sedative and hypnotic drug that was largely replaced in the mid-20th century by barbiturates and benzodiazepines.[14] Chloral hydrate is still used as a sedative prior to EEG recording because it is one of the few available sedatives that does not suppress epileptiform discharges. Its sedative and hypnotic effects appear in 20–60 min after administration and last for 60–120 min. The half-life of chloral hydrate is a few minutes but the half-life of its metabolites is longer; 8–12 h for TCE and 67 h for TCA.[4] Now it is illegal to purchase chloral hydrate in the United States without a prescription. Its use is largely restricted for sedation of children younger than 3 years of age. Melatonin is a naturally occurring hormone; its therapeutic potential may be limited by its short biological half-life, poor bioavailability, and the fact that it has numerous non-specific actions.[15] The time to reach peak plasma concentration for melatonin is 20–120 min after administration. This time for chloral hydrate is 60–180 min. The onset of action for melatonin is 30–120 min and the elimination half-life is 30–50 min.[16] It has been shown that melatonin is practically non-toxic and a short course of low doses exhibits almost no side effects in healthy people.[17] Melatonin is available as a dietary supplement without prescription in most countries including the United States and Canada.

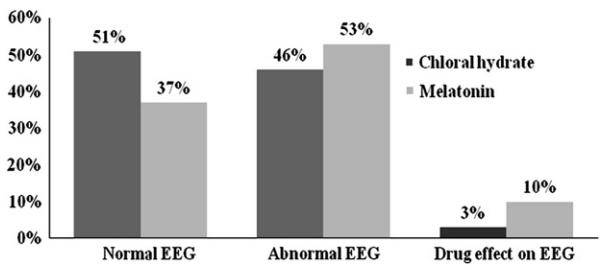

Fig. 2 – Comparison of sleep electroencephalogram (EEG) interpretation between groups of patients sedated with chloral hydrate and melatonin.

We did not find any similar study in the review of relevant literature that compares chloral hydrate with melatonin for recording sleep EEGs in children. Our study showed that the median latency of sleep induction was similar in both groups of melatonin and chloral hydrate. However more participants in the melatonin group required a second dose of sedation for sleep EEG induction. Moreover sleep duration was significantly shorter in the group of melatonin compared to the group of chloral hydrate. In addition sleepiness was significantly longer in patients sedated with chloral hydrate. The shorter sleep period and more rapid return of arousal were the advantages of melatonin for sleep EEG recording in the pediatric population.

Detection of seizure activities in the electroencephalograms was significantly higher in melatonin sleep recordings compared to chloral hydrate. The yield of epileptic discharges in the melatonin group was similar to previous studies.[18,19] The increased fast activities reported in the electroencephalogram of a few patients in our cohort sedated with chloral hydrate were typical of barbiturate effects reported in the literature.[20,21] There are reports of increased theta and alpha power in wakeful EEGs when melatonin was administered during the day.[22,23] However in a literature review we did not find anything about melatonin effects on the sleep EEGs. We found slow dysrrhythmia in the sleep EEG of children sedated with melatonin. None of the drug effects altered the interpretation of EEGs and all of them had a normal EEG report.

In conclusion melatonin might be a plausible alternative to chloral hydrate for the recording of sleep EEGs in the pediatric population. It is an attractive alternative for sleep induction without significant adverse effects and has a good yield of

detection for seizure activities. The combination of behavioral training and melatonin as another potential alternative would be an interesting subject for future investigation.

Acknowledgements

Our special thanks to Dr Marjan Dibaiyan and Behinpad Darou Corporation for providing melatonin oral liquid. We also thank the staff of the electrodiagnostic department of Children's Medical Center, Parasto Saeedi and Mitra Zamani for their cooperation in the EEG recordings and data collection.

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