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Melatonin effects on macro sleep architecture in Alzheimer's disease patients

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Original article

SUMMARY

The objective of this study was to determine the effects of 5mg. immediate release melatonin on the macro sleep architecture in eight patients diagnosed with middle to moderate Alzheimer's disease (AD). Using the Polysomnographic technique (PSG) a single-blind, non-randomized controlled placebo trial was made. The PSG was carried out according to the following order: Night 1: placebo administration; Nights 2 and 3: continuous melatonin administration (5 mg.). It was observed that the melatonin treatment during the first night of administering significantly lowered the phase 2, delta wave and REM sleep latency when compared with placebo ($P \leq .05$). Significant differences in the total time of each sleep phase were not observed; nor in the efficiency of sleep in presence of melatonin. However a tendency to the diminishment of total wake time and a rise in the total sleep time was indeed observed, especially during the second night of treatment. It was concluded that melatonin can improve sleep in patients with middle to moderate AD.

Key words: Alzheimer, sleep, melatonin.

RESUMEN

El objetivo del presente estudio fue determinar los efectos de 5 mg. de melatonina de liberación inmediata sobre la macro-arquitectura del sueño en ocho pacientes con diagnóstico de Demencia Tipo Alzheimer (DTA) de media a moderada. Utilizando la técnica polisomnográfica (PSG) se realizó un estudio simple ciego, no aleatorio, controlado con placebo. Los registros PSG se llevaron a cabo de la siguiente manera: Noche 1: administración de placebo; noche 2 y 3: administración continua de melatonina (5 mg). Observamos que el tratamiento con melatonina durante la primera noche de administración disminuyó significativamente la latencia de la fase 2, del sueño de ondas delta y el sueño de MOR al ser comparadas con el placebo ($P \leq .05$). No se observaron diferencias significativas en el tiempo total de cada fase de sueño; tampoco se observaron diferencias en la eficiencia del sueño en presencia de la melatonina. Sin embargo se observó una tendencia a la disminución del tiempo total de vigilia y un aumento del tiempo total de sueño, principalmente durante la segunda noche de tratamiento. Concluimos que la melatonina puede mejorar el sueño en pacientes con DTA de media a moderada.

Palabras clave: Alzheimer, sueño, melatonina.

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INTRODUCTION

Alzheimer's disease (AD) is the main kind of dementia presented in elderly people. It affects 35% of the population over 65 years of age in Mexico and it is the fourth main cause of death in the country, after heart diseases, cancer and diabetes.[1]

This kind of dementia starts approximately as of 55 years of age, with a progressive loss of memory, personality changes and uninhibited behavior. Additionally, cognitive functions such as language, abstract thinking, as well as people and place recognition are altered.[2] As for the basic physiological functions, it has been observed that sleep is affected in this kind of dementia. A diminishment or absence of delta sleep has been observed in patients with AD, as well as an increase in nighttime wake, a rise in daytime somnolence, and a decrease in the total nocturnal sleep time. In late stages of the disease alterations in the sleep circadian rhythm, REM sleep extended latency and a decrease in the percentage of these sleep phase have been observed.[3-6] There is enough evidence that establishes that sleep alterations are correlated with a better commitment of the memory, as well as with the decrease of the cognition. Because of this, the optimization of the handling of sleep disorders in these patients is a priority.

Damage of the neural structures and paths related to the mechanisms of sleep installation, is the most direct cause of changes in the sleep-wake cycle observed in AD. The bio-

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logical clock that has control over the circadian rhythms, including the one regarding sleep, is the suprachiasmatic nucleus (SCN).[7,8] It has been suggested that this nucleus is importantly affected in AD.[4] The SCN transmits the luminous information received by the retina toward the pineal gland where melatonin is secreted (N-methoxy-5-acetyltryptamine).[8] This indolamine is the hormone which is most related with the regulation of circadian rhythms and it has been proved that it has effects over the installation of the sleep mechanisms.[9] There is evidence which says that melatonin in people without dementia reduces latency to sleep, promotes a less fragmented temporal distribution, increases the total sleep time, its efficiency and improves its quality.[10-15]

In the last few years the use of melatonin in the treatment of alterations in the sleep-wake cycle has increased. In humans, it has been observed that doses of 3 to 5mg. maintain the synchronization of the circadian rhythm in a 24-hour cycle, improving sleep as well.[9] However, the existent information about the effects of melatonin over sleep on patients with diagnosed AD is limited. It has been proposed that this hormone in people with AD extends the sleep periods and improves the sleep-wake cycle.[16,17] However, the effects of melatonin over the macro architecture of sleep in AD are not known with exactitude, since most of the trials made until now have used techniques such as actimetry which generates information about the amount of movements of the patients in the 24-hour period, and the sleep questionnaires, which allow for the subjective appreciation of the patient regarding sleep habits and the quality of the sleep itself to be known. Nevertheless, the polysomnographic technique (PSG) is currently the most accurate scientific standard that exists for optimally evaluating the temporal distribution of the different stages of sleep and wake. This technique also permits exploring the action of the drugs on the cortical activity, because it implicates the register of the electroencephalographic activity (EEG). Regarding this, the goal of this study was to determine the effects of the oral administration of 5mg. of melatonin upon the temporal organization of the nocturnal sleep stages (macro architecture), in persons diagnosed with middle to moderate AD, using the PSG technique.

MATERIALS AND METHODS

Subjects

Eight patients who attended to the Neurology Department of the "Samuel Ramírez Moreno" Hospital, in Mexico City, were studied. The patients were in average 65 years of age. The AD diagnosis was made through a neurological exploration, which allowed for establishing a dementia syndrome diagnosis. Paraclinical tests were previously run, with the objective of making the diagnosis of reversible dementia. For this procedure, the following measurements were applied: hematic biometry, blood chemistry test, hepatic and thyroid function tests, simple contrast CAT scan, evaluation of the ischemic factors in dementia through the Hachinski scale, as well as an electroencephalography trial.

Once all the reversible dementias had been excluded, a scale (designed in our laboratory) for evaluating the superior mental functions was applied, in which the minimal deterioration of language, praxis and gnosis was supposed to be observed by using the criteria of the ailments of probable or possible AD set by the Alzheimer's Disease Association and related disorders (NINCDS-ADRDA).[18] The severity of the dementia was determined through the Mini-mental state examination,[19] and it was considered as criteria of inclusion that all subjects should obtain an average score corresponding to the severity from middle to moderate (10-22 points). Additionally, as criteria of inclusion, it was considered that the subjects presented sleep alterations, which was evaluated through a clinical interview designed in our laboratory. This interview was applied to the persons who habitually spend the night with the patients (caregivers). None of the patients previously received pharmacological treatment made of acetylcholine inhibitors or any other drugs with psychotropic action.

Informed consent of the patient's caregivers was obtained via external consult. According to the guidelines established in the Helsinki Declaration and the guidelines of the *National Institutes of Health* of the United States of America, the study was approved by the ethics in human investigation commission of the National Institute of Psychiatry Ramón de la Fuente Muñiz.

Study design

A single-blind, non-randomized controlled placebo trial was made. Four nocturnal PSG registers were made to each patient, using the first night as a period of habituation to the register conditions, a night in which placebo was administered (P) and during the following two nights (M1-M2) 5mg. of melatonin were administered orally, in a single dose. Immediate liberation melatonin was used. Both the melatonin and the placebo were administered one hour before the patient went to sleep (approximately at 9:00 pm). The order of the treatments (P and M1-M2) was counterbalanced. The PSG registers of M1-M2 treatments were made with a one week interval from the placebo session. For statistical purposes, all patients were their own control, and all of them were part of the different groups of experimental design (P and M1-M2).

Evaluation methods

PSG registers. Electrodes were placed in the bipolar derivations O1-O2, C4-A2, C3-A1, T3-F7, T4-F8, F3-F4 of the international system 10-20 for human EEG. Electrodes were also

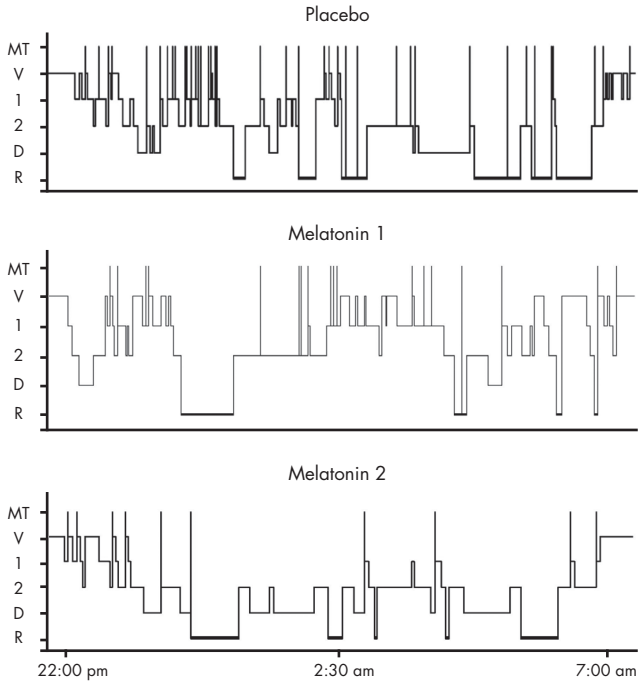

Figure 1. Representative hypnograms of sleep macro architecture observed in placebo condition (P) and in the first (M1) and second (M2) night of melatonin administration. The image shows the case of only one of our patients. Each one of the stages is indicated on the Y axis; the X axis represents the nine hours of PSG register. The horizontal lines in the graphic represent the time of each sleep and wake stage. The vertical lines indicate the phase change. Mt: movement, 1: phase 1 of non-REM sleep, 2: phase 2 of non-REM sleep, D: DELTA sleep, R: REM sleep.

placed, superficially, in both ocular canthus to obtain the electrooculography (EOG) and were placed in the same way in the *mentalis* muscle to obtain the electromyogram (EMG). Nine continuous hours of PSG register were recorded that began at 22:00 pm and culminated at 7:00 am of the next day. The records were made in a chamber especially designed for PSG in humans, sound-absorbing, electrically isolated and with an audio and video closed circuit. A digital system for PSG was used (Grass, Co USA, model 15), with a sample range of 512 Hz, using a band-pass filter of .1 to 35 Hz.

The temporal distribution of sleep and wake behavioral ranges was in electroencephalographic periods of 30 seconds, as of the international criteria established by Rechtschaffen and Kales for PSG.[20] The sleep macro architecture was analyzed as of the sleep latencies; which was considered as the time (min) which is taken until the first episode of each sleep phase appears. The total time of sleep in each sleep phase and its efficiency was analyzed as well, which was the percentage of total sleep time of the register.

Statistical analysis

The aforementioned variables were statistically compared using Student's t-test. Comparisons were made between the conditions P and M1, and P and M2. To run the analysis, the software SigmaPlot 11.0 was used. The differences were considered statistically significant with $p \leq .05$.

RESULTS

Qualitative observations

When visually evaluating the temporal distribution of the different sleep and wake stages, it was observed that two of our patients did not present delta sleep during the night of habituation and placebo. However, this is counteracted in presence of melatonin, due to the fact that all our patients presented various episodes of delta sleep distributed in the eight hours of study, during both nights in which melatonin was administrated. During the placebo nights, a great amount of short body movements, which mainly fragment the continuity of non-REM sleep, was observed in all our patients. Nevertheless, these movements progressively decreased through the nights of melatonin treatment (figure 1). Bruxism was also observed during the non-REM sleep in three of our patients in all the nights of the register.

Quantitative analysis

Table 1 shows the results of the statistical analysis. Figures 2, 3 and 4 graphically represent theses values, which are expressed as the average ± the standard deviation (SD). The results of the t-tests show that between the latencies of the conditions P and M1 there are statistically significant differences, with a diminishment of the installation time in the

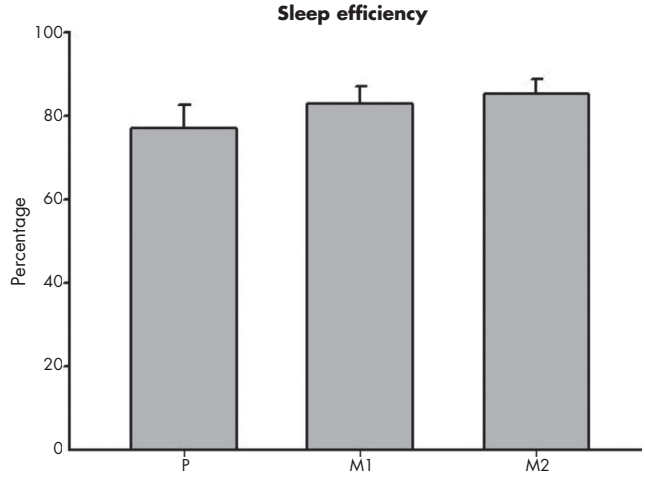

Figure 2. Latencies of the first episode of the different sleep phases. X axis= placebo condition (P), first night of melatonin administration (M1) and second night of melatonin administration (M2). Y axis= time (min) in which the first episode of each sleep phase appears since the beginning of the PSG register (9:00 pm approx.) *Significant differences between P and M1.

Table 1. Numeric values of sleep macro architecture. Differences between placebo conditions (P) and melatonin 1 (M1), and placebo and melatonin 2 (M2). The values are expressed as the average ± standard deviation (SD). The probabilities (p) and t values of the group comparisons using Student's t-test are shown. (n=8). The parameters are expressed in minutes, except efficiency, which is represented as a percentage. The differences were considered statistically significant with a $p \leq .05$. *Significant differences between P and M1.

	Placebo		Melatonin 1		Melatonin 2			
	Mean	SD	Mean	SD	Mean	SD	t	P
Efficiency %	77.22	15.76	83.06	11.44	85.36	10.21		
Latencies (min)								
• Phase 1	17.93	10.24	15.43	9.31	15.43	9.31		
• Phase 2	34.75	24.15	15.25*	5.95	30.43	20.08	2.217	.044
• Delta sleep	210.33	169.12	33.71*	15.69	94.58	9.14	2.988	.017
• REM sleep	172.40	109.80	76.50*	30.50	128.93	85.82	2.380	.032
Total time (min)								
• Wake	89.93	57.57	72.75	50.12	57.75	55.39		
•Phase I	54.87	37.34	66.50	35.78	67.37	75.71		
• Phase 2	221.87	86.69	248.06	78.83	212.87	106.83		
• Delta sleep	29.00	36.41	29.50	18.79	63.12	51.86		
• REM sleep	56.66	29.37	76.50	30.50	85.00	39.99		

* Significant differences between P and M1.

first episodes of the phase 2 of non-REM sleep (p=0.044), delta sleep (p=0.017) and REM sleep (p=0.032) being observed (figure 2). However, there were no significant different of the sleep latencies between the conditions P and M2. Regarding sleep efficiency, no significant differences related to melatonin in any of the two nights of treatment were observed (figure 3).

As to the total time of each sleep phase, the variations observed were not statistically significant, however, results show a tendency towards the increase of phase 1 in conditions M1 and M2, and an increase of the total time of phase 2 was observed in condition M1 as well. Delta sleep increased its values mainly during condition M2. REM sleep showed a progressive increase in its values through both melatonin conditions, as well as the total time of wake, which also decreased, mainly in condition M2 (figure 4).

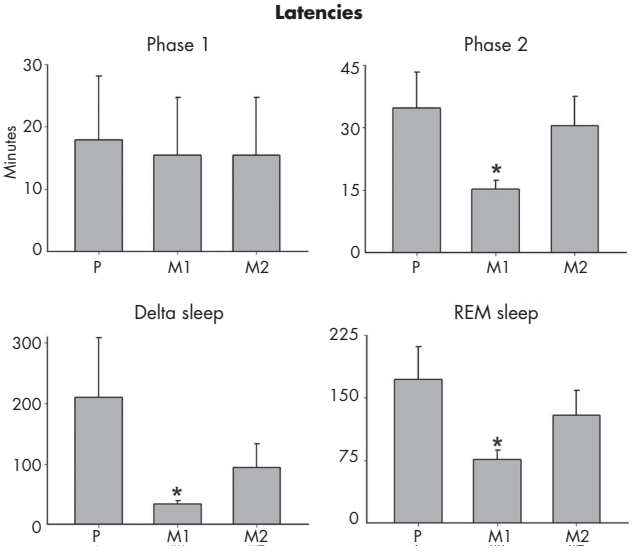

Figure 3. Sleep efficiency. X axis= placebo condition (P), first night of melatonin administration (M1) and second night of melatonin administration (M2). Y axis= Percentage of sleep of the total register time. No statistically significant differences related to melatonin were observed.

DISCUSSION

In this study, it was observed that melatonin significantly diminishes the installation latency in phase 2 of non-REM sleep, delta sleep and REM sleep in patients with AD, mainly during the first night of administration. A tendency to the diminishment of the total wake time and an increase in the total sleep time was observed as well, especially during the second night of administration.

As to the diminishment observed in the latencies, it was noticed that these get close to the normal time previously reported in geriatric non-dementia patients.[21] Additionally, the effect of rapid installation of sleep provoked by melatonin upon non-dementia geriatric patients has been previously documented. It was observed that 3mg. doses favor the rapid installation of non-REM sleep,[17] as it was observed in the current study. These results suggest that structures like SCN, as well as the thalamic-cortical circuits and structures of the brain stem in charge of sleep control and regulation, even with middle to moderate AD, are capable of reacting to the cascade of events that melatonin performs to make sleep installation easier.

The neurobiological mechanism which explains sleep induction produced by melatonin is not known accurately nowadays, however, there are various works that support

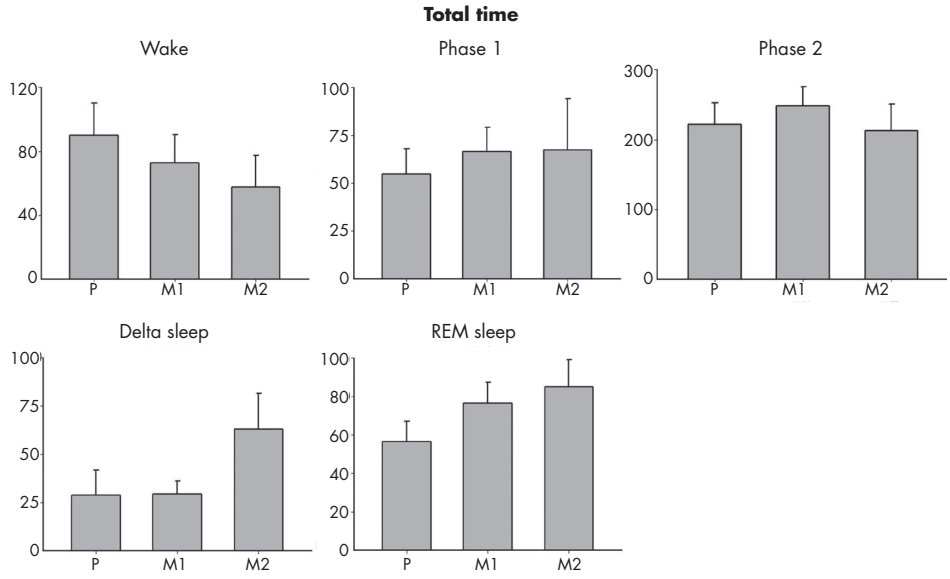

Figure 4. Total time of the different sleep and wakeful phases. X axis= placebo condition (P), first night of melatonin administration (M1) and second night of melatonin administration (M2). Y axis= total time (min) of each sleep and wake phase. No statistically significant differences related to melatonin were observed.

the idea that the aforementioned hormone induces sleep through the modulation of GABA receptors. It has been suggested that pharmacological doses of melatonin (≤1mg.) can directly interact with benzodiazepine receptors, which apply their effects through GABAergic modulation.[21-25] This suggests that the interaction of melatonin with the GABAergic system could be related to the activation of neurophysiologic mechanisms of sleep installation.

Additionally, our results show for the first time that melatonin has effects over REM sleep installation in people with AD. In this regard, it is know that the mechanism which activates the various components of REM sleep is formed by a group of neurons of the dorsal protuberance of a cholinergic nature.[26-28] However, it has been described that a diffuse group of neurons of the ventrolateral preoptic area (VLPO) is capable of inducing REM sleep through its projections that inhibit the expression of monoamines of the dorsal raphe (serotoninergic) and the *locus coeruleus* (noradrenergic).[29-31] The inhibitory projections toward the VLPO by the histaminergic, serotoninergic and noradrenergic components of the wake system, use the GABA which is present in 60% of the neurons of the VLPO. If melatonin modulates the GABAergic activity, thus is it possible that the neurons of the VLPO are activated by this hormone with a consequent suppression of wake, and at the same time making easier the installation and expression of REM sleep. The neurons of the VLPO are denominated sleep-active neurons (REM-on), which innervate the areas which promote wake, such as the tuberomammilary nucleus, the lateral hypothalamus, the dorsal raphe, the dorsolateral tegmentum (DLT) and the pedunculopontine tegmentum (PPT).[30,31] It is likely that the increase of sleep-active neurons activity, of a GABAergic nature, inhibit the areas which promote wake, and hence induce REM sleep.

It is of interest to point out that the action that melatonin has on the sleep of our patients could have therapeutic benefits on memory and learning deficits, characteristic of AD, especially for the performance of this tasks the day following the administration of the drug, because it has been proved that REM sleep and phase 2 non-REM sleep are closely related to different cognitive processes which are underneath memory and learning fixation and maintenance.[32-34] Additionally, during REM sleep, cell restoration processes that are not observed in any other moment during the sleep-wake cycle take place. On the other side, it is of interest to point out that the secretion of growth hormones and the synthesis of neurotrophins[21] both take place during delta sleep; these processes of physiological restoration are very important in AD.[35]

It has been suggested that sleep is controlled by two systems. On the one hand, circadian rhythm; which is the natural tendency to sleep that varies throughout the day and appears mainly in REM sleep. On the other hand, there is sleep homeostasis, which makes man feel somnolence during the night.[36] Delta sleep faithfully reflects this homeostatic sleep control, because it has been proved that every situation that involves an increase in the wake previous to the sleep period will involve an increase in the proportion of delta sleep.[24,36-39] Our results suggest that melatonin has action over both processes, due to the fact that a tendency towards the increase of the total time of delta sleep, as well as

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diminishment of the latency of this sleep phase and of REM sleep can be observed. These results indicate that melatonin helps the organism to start the restoration and resting processes at the most adequate hour of the natural light-darkness cycle, which has a great therapeutic value.

The notable tendency towards the increase of total sleep time and the diminishment of nocturnal wake, especially in the second night of administration, indicates that melatonin can promote a larger amount of nocturnal sleep, which has a direct impact on the life quality of the patients and that of the people who live and take care of them, since these people are being constantly deprived of sleep because of the distinct disorders of the sleep-wake cycle in patients with AD.

Additionally, our results point out that melatonin possesses a direct action over the mechanisms of sleep installation in general, but not over those of maintenance, because sleep efficiency does not show significant changes in presence of melatonin. Nevertheless, these limited effects of the drug could be caused due to the type of liberation used. Due to melatonin having a medium-short life span, prolonged liberation might have the possibility of activating the brain receptors through the night, thus improving sleep efficiency, thus it is suggested that prolonged-release melatonin should be used in future studies, with the objective of determining if this type of presentation is convenient to obtain better therapeutic effects in patients with AD. Performing more complete PSG studies is also suggested, in which register of the respiratory activity and electrocardiogram (ECG) shall be included. Performing the spectral analysis of the EEG activity in the presence of melatonin is considered necessary, because it has been proved that this kind of analysis allows for the determination of precise homeostatic effects that this hormone performs during sleep.[38]

CONCLUSIONS

In the current study it was observed that 5mg. of melatonin make sleep installation in people with middle to moderate AD easier. Our result suggests that melatonin could be used as a therapeutic option to treat sleep problems in people who suffer from this kind of dementia.

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