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ORIGINAL ARTICLE

Melatonin treatment stabilizes chronobiologic and cognitive symptoms in Alzheimer's disease

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Abstract

OBJECTIVES: A retrospective study on the efficacy of melatonin in treatment of sleep and cognitive disorders of Alzheimer's disease was conducted.

METHODS: Fourteen patients (8 females, 6 males), mean ± S.D. age 72 ± 9 years were included. All patients received 9 mg gelatin melatonin capsules p.o. daily at bedtime for 22 to 35 months. Overall quality of sleep was assessed from sleep logs filled in by the patients or their caretakers. Neuropsychological evaluation was performed by Functional Assessment Tool For Alzheimer's Disease (FAST), Mini-Mental, Alzheimer's Disease Assessment Scale (ADAS), and Mattis' and Blessed's scales. At diagnosis, all patients had cognitive and neuroimaging alterations (cortical and bitemporal atrophy) compatible with different evolutionary stages of the disease.

RESULTS: At the time of assessment, a significant improvement of sleep quality was found in all cases examined. There were no significant differences between initial and present evaluation in scores of FAST, Mini-Mental, and ADAS, and of Mattis' and Blessed's scales. Clinically, the patients exhibited lack of progression of the cognitive and behavioral signs of the disease during the time they received melatonin. Sundowning was no longer detectable in 12 patients and persisted, although attenuated, in 2 patients.

CONCLUSION. The results suggest that melatonin can be useful for treatment of Alzheimer's disease.

Introduction

In recent years the hypothesis on a possible therapeutic relevant effect of melatonin in Alzheimer's disease (AD) has been entertained. Support to this hypothesis derived from in vitro data indicating that melatonin protects neurons against β-amyloid toxicity and inhibits amyloid formation [1], prevents β-amyloid-induced lipid peroxidation [2], alters the metabolism of the β-amyloid precursor protein [3] and prevents the oxidative damage by β-amyloid of mitochondrial DNA [4].

Treatment of demented patients having sleep disorders with melatonin (3 mg p.o.) improved significantly "sundowning," i.e. the episodes of agitated behavior at night, although sleep quality remained unmodified at the low doses employed [5]. In a case report of two monozygotic twins suffering from AD of 8 years of evolution (one of them was treated with melatonin, 6 mg p.o. for 36 months), evolution of the disease was halted in the melatonin-treated subject, as indicated by a stable impairment of mnesic function and a substantial improvement of sleep quality and reduction of sundowning [6]. As a continuation of these studies, we now report the results of a retrospective study on the efficacy of a 9 mg melatonin dose, given daily for periods varying from 22 to 35 months, to treat sleep and cognitive disorders in 14 AD patients. The results presented herein support the existence of a beneficial, therapeutic effect of melatonin in AD.

Material and Methods

Fourteen patients (8 females, 6 males) were included in the study. The participants or their legal caretakers gave informed consent for the study. The mean ± S.D. age of patients was 72 ± 9 years. The following exclusion criteria (assessed in structured interviews, [7]) were used: presence of any kind of organic disorder, presence of any kind of psychiatric disorder other than AD, past history of neurological disorder, alcohol abuse or addiction to other drugs, or heavy smoking habits.

All patients were treated with melatonin (3 mg-gelatin capsules, Melatol^{R}, Elisium S.A., Buenos Aires) in doses of 9 mg p.o. at bedtime daily for variable periods, ranging from 22 to 35 months. Other medication received is quoted in Table I. In addition, patients #13 and #14 received 25 mg/day thioridazine because of the behavioral and sleep disorder; both patients interrupted thioridazine treatment after 5 and 24 months of starting melatonin treatment, respectively.

Overall quality of sleep and daytime alertness were assessed from structured clinical and from sleep logs filled in by the patients or their caretakers, who assessed the quality of sleep graphically in a scale rated from 0 to 10 [5]. Neuropsychological evaluation of the patients was performed by the Functional Assessment Tool For Alzheimer's Disease (FAST) [8], Mini-Mental, Alzheimer's Disease Assessment Scale (ADAS) [9] and Mattis' [10] and Blessed's scales [11]. Results were statistically analyzed by a paired non-parametric Wilcoxon's test.

Results

Neuropsychological evaluation at diagnosis indicated a primary impairment of mnesic function of a varying degree (Table II). All patients had cognitive and neuroimaging alterations (cortical and bitemporal atrophy) compatible with different evolutionary stages of the disease.

After varying periods of time of treatment with melatonin, as quoted in Table I, a significant improvement of sleep quality was found in all cases, the differences with the initial assessment being highly significant ($p = 0.001$, Wilcoxon's test) (Table II). Sundowning, diagnosed clinically in all patients examined, was no longer detectable in 12 patients, and persisted (although attenuated) in patients #8 and #9. Neuropsychological evaluation by FAST, Mini-Mental and ADAS, and by Mattis' and Blessed's scales indicated absence of significant differences between initial and present state of evolution of the disease (Table II).

The neurological exam at the time of assessment indicated that the patients exhibited lack of progression of the cognitive and behavioral signs of the disease. This should be contrasted with the significant deterioration of clinical conditions of the disease expected from patients after 1-3 years of evolution of AD (see e.g., [12-14]). No side effects of melatonin were detected in the population of patients examined.

Patients received melatonin for 22 to 35 months, as stated in Table 1. For every parameter assessed the initial (I) and present value (F) are given. Differences in sleep quality between initial and present assessment were significant ($p = 0.001$, Wilcoxon's test)

Discussion

The foregoing preliminary observation on a differential evolution of AD in 14 patients treated from 22 to 35 months with 9 mg/day of melatonin suggests that melatonin can be therapeutically valuable in AD. The improvement was found both in sleep-related and cognitive symptoms of the disease.

As far as sleep, melatonin treatment was par-

Table I. Demographic data

#	Age	Sex	AD evolution treatment	Melatonin (months)	Other treatment
1	58	F	34	25	-
2	80	F	50	23	-
3	76	F	70	30	Nifedipine (90 mg/day), Levodopa (200 mg/day)
4	63	M	42	30	Enalapril (10 mg/day)
5	77	M	48	23	Vitamin E (800 IU/day)
6	78	F	65	30	Enalapril (20 mg/day), Alprazolam (1 mg/day), Allopurinol (100 mg/day), vitamin E (400 IU/day)
7	68	M	38	25	Nifedipine (20 mg/day), Atenolol (50 mg/day)
8	68	F	46	22	Vitamin E (400 IU/day)
9	82	F	70	30	Levodopa (500 mg/day) Clozapine (70 mg/day)
10	53	M	80	24	Vitamin E (800 IU/day)
11	77	F	30	22	-
12	66	M	82	24	-
13	69	F	72	30	-
14	80	M	70	35	-

Table II. Effect of melatonin treatment (9 mg, p.o.) on subjective assessment of sleep quality and scores of FAST, Mini-Mental, and ADAS, and Mattis' and Blessed's scales in 14 patients with AD.

#	Sleep Quality		FAST		Mini-Mental		ADAS Cognition		Mattis' Scale		Blessed's Scale	
	I	F	I	F	I	F	I	F	I	F	I	F
1	2	7	5	4	18	18	27	26	104	105	15	16
2	3	7	6a	5	15	15	29	30	110	107	20	19
3	2	8	7	6c	3	3	-	-	-	-	25	26
4	2	6	6a	5	24	23	14	15	123	121	20	19
5	2	5	5	4	20	19	25	25	106	107	21	21
6	4	6	3	2	19	19	26	25	104	106	15	16
7	2	5	4	3	24	25	13	11	125	127	13	15
8	3	6	4	4	19	19	26	25	105	108	16	16
9	3	6	6c	6c	5	5	-	-	-	-	25	23
10	2	5	6c	7a	2	2	-	-	-	-	25	26
11	3	6	2	2	24	25	14	13	124	125	15	16
12	2	5	6a	6c	9	9	-	-	-	-	20	18
13	3	5	4	5	9	9	-	-	-	-	18	17
14	2	8	6b	6b	10	10	-	-	-	-	16	16

ticularly effective to reduce sundowning agitation, found in about half of the patients with dementia and which is the most common cause of institutionalization of the demented geriatric patient. So far, management of sundowning includes restriction of daytime sleep, exposure to bright light and social interaction schedules during the day [15]. Recently, we reported that melatonin (3 mg p.o. at desired bedtime for 21 days) ameliorated sundowning in 7 out of 10 dementia patients having sleep disorders [5]. In agreement to those previous findings, all patients in the present series treated with a greater melatonin dose (9 mg) did improve sleep quality and reduced or eliminated sundowning after melatonin.

Another important observation in the subjects studied was the halted evolution of the cognitive and mnesic alterations expected in comparable populations of patients not receiving melatonin (see e.g., [12-14]). Although it cannot be stated at the present time whether this was a consequence of melatonin

improvement in sleep-wake rhythms or an effect of melatonin treatment on any primary mechanism of AD, a putative beneficial effect of melatonin on AD pathophysiology is not without experimental basis. It is known that β-amyloid is a major constituent of senile plaques that occurs in the brains of AD patients. Cell culture studies have shown that high concentrations of β-amyloid are toxic and damage biological macromolecules. The amyloid in senile plaques is composed of an β amyloid peptide of 39-43 amino acid residues derived from a larger β-amyloid precursor protein (β APP). It is generally held that β-amyloid plays a central role in the progressive neurodegeneration observed in AD [4]. Important pathologic properties of this protein, such as neurotoxicity and resistance to proteolytic degradation, depend on the ability of β-amyloid to form β-sheet structures or amyloid fibrils.

In vitro, melatonin protects neurons against β-amyloid toxicity, interacts with β-amyloid 1-40 and β-amyloid 1-42 and inhibits the progressive formation of β-sheets and amyloid fibrils [1, 16]. Melatonin also impairs the secretion of soluble derivatives of β APP lacking the cytoplasmic tail [3]. All these effects of melatonin have been attributed to its antioxidant properties. Indeed, melatonin neutralizes oxygen-derived free radicals as well as carbon-centered free radicals [17]. Likewise, melatonin augments the activities or increases the levels of mRNA of enzymes that improve the total antioxidative defense capacity, like glutathione peroxidase, copper-zinc superoxide dismutase or manganese superoxide dismutase [18]. Melatonin effectively reduced the lipid peroxidation induced in vitro by β-amyloid or aluminum [2] and the oxidative damage of mitochondrial DNA caused by β-amyloid protein [4].

Summarizing, the present retrospective trial suggests that melatonin can be helpful in AD. Melatonin treatment at relatively moderate pharmacological doses can help to ameliorate behavior disorders and to halt cognitive impairment in elderly patients with dementia. To what extent this is due to an effect of melatonin on β-amyloid-related processes or is the consequence of an improvement in sleep quality and reduction of sundowning agitation awaits further investigation.

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REFERENCES

1 Pappolla M, Bozner P, Soto C, Shao H, Robakis NK, Zagorski M, et al. Inhibition of Alzheimer β-fibrillogenesis by melatonin. J Biol Chem 1998; **273**:7185–7188.
2 Daniels WM, Van Rensburg SJ, Van Zyl JM, Taljaard JJ. Melatonin prevents β amyloid, induced lipid peroxidation. J Pineal Res 1998; **24**:78–82.
3 Song W, Lahiri K. Melatonin alters the metabolism of the β-amyloid precursor protein in the neuroendocrine cell line PC12. J Mol Neurosci 1997; **9**:75–92.
4 Bozner P, Grishko V, Ledoux SP, Wilson GL, Chyan YC, Pappolla MA. The amyloid β-protein induces oxidative damage of mitochondrial DNA. J Neuropathol Exp Neurol 1997; **56**:1356–1362.
5 Fainstein I, Bonetto AJ, Brusco LI, Cardinali DP. Effects of melatonin in elderly patients with sleep disturbance. A pilot study. Current Ther Res 1997; **58**:990–1000.
6 Brusco LI, Márquez M, Cardinali DP. Monozygotic twins with Alzheimer's disease treated with melatonin. Case report. J Pineal Res 1998; **25**:260–263.
7 Kaplan HI, Sadock BJ, Grebb JA. Synopsis of psychiatry, 7th ed. Baltimore: Williams & Wilkins; 1994.
8 Auer S, Reisber B. The GDS/FAST staging system. Int Psychogeriatr 1997; **9** Suppl 1:167–171.
9 Mohs RC, Cohen L. Alzheimer's disease assessment scale (ADAS). Psychopharmacol Bull 1988; **24**:627–628.
10 Mattis S. Dementia rating scale professional manual, Psychological Assessment Resources: Odess, FLA; 1988.
11 Blessed G, Tomlinson BE, Roth M. Blessed-Roth dementia scale (DS). Psychopharmacol Bull 1988; **24**:689–692.
12 Katzman R, Kawas C. The epidemiology of dementia and Alzheimer Disease. In: Terry RD, Katzman R, Bick KL, editors. Alzheimer disease, New York: Raven Press; 1994. p. 105–122.
13 Jost BC, Grossberg GT. The evolution of the psychiatric symptoms in Alzheimer's disease: A natural history study. J Am Geriatr Soc 1996; **44**:1078–1081.
14 Rogers SL, Friedhoff LT. Long-term efficacy and safety of donazepil in the treatment of Alzheimer's disease: An interim analysis of the results of a US multicentre open label extension study. Eur Neuropsychopharmacol 1998; **8**:67–75.
15 McGaffigan S, Bliwise DL. The treatment of sundowning: A selective review of pharmacological and nonpharmacological studies. Drugs & Aging 1997; **10**:10–17.
16 Pappolla MA, Sos M, Omar RA, Bick RJ, Hickson-Bick DL, Reiter RJ, et al. Melatonin prevents death of neuroblastoma cells exposed to the Alzheimer amyloid peptide. J Neurosci 1997; **17**:1683–1690.
17 Reiter RJ, Tang L, Garcia JJ, Muñoz Hoyos A. Pharmacological actions of melatonin in oxygen radical pathophysiology. Life Sci 1997; **60**:225–271.
18 Kotler M, Rodríguez C, Sainz RM, Antolin I, Menéndez Pelaez A. Melatonin increases gene expression for antioxidant enzymes in rat brain cortex. J Pineal Res 1998; **24**:83–89.