Research Article

A cross-sectional report on the use of high doses of melatonin in humans

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ABSTRACT

The administration of melatonin in chronobiotic doses (≤10 mg daily) is a common procedure in clinics. In addition, research in animals has led to greater awareness on the potentiality of melatonin as an antioxidant, immunological and mitochondrial regulator and anti-inflammatory compound. Doses allometrically derived from animal studies correspond to 75 to 112.5 mg daily range for a 75 kg human adult. In view of the absence of toxicity of melatonin in phase 1 pharmacological studies with doses up to 100 mg in normal volunteers, we regularly use melatonin in this dose range to treat sleep disorders in aged patients to prevent age-related comorbidities. In an observational, analytical, retrospective, cross-sectional study of clinical history data from a closed population of patients taking melatonin in doses equal to or greater than 40 mg/day of melatonin for various sleep disorders, 80 patients (74.2 % female, mean age 74 years ± 9.26) were included. The indication of melatonin doses varied between 40 and 200 mg per day, with a mean of 76.56 mg ± 33.58 mg daily. The main reason for indication was complaints of disorders in falling asleep or maintaining sleep with melatonin doses varying depending on the comorbidities clinically detected. The 59 % of patients received treatment for more than 4 years. Laboratory variables related to liver function remain within the normal range after melatonin administration regardless of the dose employed. No relation was also found between melatonin dose and concomitant pharmacological treatment. The results advocate for the safe use of melatonin in higher doses than those commonly employed.

Key words: Chronobiotic, cytoprotection, high melatonin dose, sleep

1. INTRODUCTION

Due to the interest in immune health sparked by the COVID-19 pandemic and its lasting effects on mental health and sleep disorders, the clinical use of melatonin has become a popular topic of discussion among the scientific community as well as in the media. Melatonin is a commonly used dietary supplement for maintaining healthy sleep (1–3). In addition, research over the past decade has led to greater awareness on the potentiality of melatonin use as an

antioxidant, immunological and mitochondrial regulator and anti-inflammatory compound in non-communicable diseases (4–8) as well as in COVID-19 pandemics (9–12).

In Argentina, the National Administration of Medicines, Food and Medical Technology (ANMAT) approved melatonin (3 mg capsules or tablets) as an over-the-counter drug in 1995. In 2017, ANMAT authorized a prolonged-release preparation of 2 mg of melatonin (Circadin^{R}) as a prescription medication. Although ANMAT cannot authorize the use of a drug for an indication that is not listed in the package leaflet, it does not mean that the indication of an approved drug for other clinical situations is prohibited. According to ANMAT, the out-of-prospect prescriptions are "the sole responsibility of the attending physician, who performs them in the full exercise of their professional activity, based on their experience and available scientific knowledge…" for which in Argentina a prescription for high doses of melatonin is required, while in the United States melatonin is free for sale (13).

A retrospective cross-sectional study of data from a closed population of 110 adult patients treated with melatonin (46.33 ± 34.1 mg/day) analyzed until the onset of COVID-19 pandemic indicated COVID-19 infection in 15 patients (13.5%). Among them 5 were required hospitalization, and only one of them had severe pneumonia with no deaths due to COVID-19 recorded (11). Since national records the lethality rate in older adults at that moment was 10.5% the results were consistent with a preventive effect of melatonin in the COVID-19 pandemic.

The administration of melatonin in chronobiotic doses (less than 10 mg daily) is a common procedure in clinics. However, human equivalent doses allometrically derived from animal studies are in the 1.0 – 1.5 mg/kg/day range for a 75 kg human adult (75 to 112.5 mg daily), a dose rarely used clinically (14–19). In view of the absence of toxicity of melatonin in phase 1 pharmacological studies with doses up to 100 mg in normal volunteers (20, 21), we regularly use melatonin in this dose range to treat sleep disorders in aged patients and to prevent comorbidities. In the present study we analyze a number of variables in patients receiving doses equal to or greater than 40 mg in comparison to those who received 80 or more mg daily at bedtime, including clinical laboratory tests and use of other pharmacological or non-pharmacological treatments in both populations. The results advocate for the safe use of melatonin in higher doses than those commonly employed.

2. PATIENTS AND METHODS

This is an observational, analytical, retrospective and cross-sectional study. Clinical history data from a closed population of the Italian Hospital of Buenos Aires were analyzed. Population was evaluated and treated in the Sleep Medicine Section with melatonin for various sleep disorders during the period from January 1, 2019 to December 31, 2023. Registered in Registry of Research Protocols of Buenos Aires (PRISSA) number 13572.

Inclusion criteria: Adult patients over 47 years of age, with the hospital's own coverage (closed population), treated with fast release melatonin at bedtime for various sleep disorders. Reasons for which treatment was indicated included insomnia (sleep disorders falling asleep; disorders in sleep maintenance and/or early awakening) - COMISA [insomnia associated with apneas with or without treatment of continuous positive airway pressure (CPAP)]; REM sleep parasomnias (REM sleep behavior disorder) or various circadian rhythm disorders. The doses employed varied from 40 to 200 mg / day depending on age and the comorbidities clinically detected. A minimum compliance of 4 months of treatment with the selected dose was required.

The clinical evaluation of patients after 4 months and the request for prescription for more than a year were taken parameters of therapeutic success and a criterion for further treatment.

Concerning variables related to liver function, we evaluated results of tests performed at least 3 months after the start of treatment with melatonin. Variables related to pharmacological and non-pharmacological treatments included the use of benzodiazepines, Z drugs, antidepressants with hypnotic action, antipsychotics and alpha 2 calcium channel ligands. Other drugs that can influence sleep such as beta-blockers and lipid-lowering agents and a non-pharmacological treatment CPAP were also considered.

Results on quantitative variables were expressed as mean ± standard deviation, while qualitative variables were expressed as frequency and percentage. To compare qualitative variables, we used chi square. To describe groups, the trend and distribution measures were used. For quantitative variables, Pearson correlation was used to compare them. To compare qualitative and quantitative variables, ANOVA was used. The statistical analyses were performed by SPSS 18 (Chicago SPSS Inc.) A $p < 0.05$ was considered significant.

3. RESULTS

Eighty patients with an age range between 47 and 98 years (mean 74 years ± 9.26) were included. The indication of melatonin doses varied between 40 and 200 mg per day, with a mean of 76.56 mg ± 33.58 mg daily. The 55% of patients received treatment for more than 4 years. The general characteristics of the population are summarized in Table 1.

Table 1: General characteristics of the study population.

	N= 80	
	n	%
Daily melatonin dose 40 to 79 mg	37	46.2
Daily melatonin dose 80 a 200 mg	43	53.8
Time on melatonin treatment		
Less than 1 year	14	17.4
1 to 3 years	21	26.2
4 years or more	45	56.2
Reason for indication of melatonin		
Insomnia or fragmented sleep	77	96.2
REM Behavior Disorder	3	3.80

The majority of patients were female (71.2%). The 35% used CPAP for the treatment of breathing disorders during sleep.

In Table 2 we compare the laboratory characteristics between patients treated with lower and higher doses of melatonin. The results indicate that there was no significant association of the analyzed parameters of liver function and the analyzed lipid profile with melatonin dose. Moreover, the observed values were in the range of normal values for the methods employed.

Table 2. Comparison of laboratory analysis variables studied according to melatonin doses.

Variables	Normal values	N=80				
		Melatonin dose 40 to 79 mg/day N=37		Melatonin dose 80 to 200 mg/day N= 43		
		Mean	SD	Mean	SD	*P*
Average dose of melatonin		46.62	7.82	102.33	24.48	0.00
Age		72	9.09	75	9.30	0.15
Variable measured						
GOT (glutamic oxaloacetic transaminase)	10-42	18.24	4.07	18.71	5.66	0.69
GPT (glutamic pyruvic transaminase)	10-40	16.47	8.69	17.29	10.19	0.72
ALP (alkaline phosphatase)	31-100	63.94	15.87	68.35	18.66	0.30
Total bilirubin	0.10 – 1.40	0.69	0.30	0.61	0.25	0.25
Direct bilirubin	0.00 – 0.40	0.14	0.09	0.17	0.17	0.37
Total cholesterol	< 200-239	189.72	61.81	183.88	42.75	0.65
Triglycerides	< 150-199	129.96	54.37	123.00	67.34	0.67
HDL cholesterol	≥ 40	51.54	11.35	56.96	13.33	0.12
LDL cholesterol	< 110-129	113.29	63.12	105.04	45.98	0.59

Expression of results and methodology employed for the variables measured included GOT (IU/L), GPT (IU/L), ALP (IU/L), measured with kinetic UV method; total bilirubin (mg/dL), direct bilirubin (mg/dL), measured with diazo method; total cholesterol (mg/dL), triglycerides (mg/dL) measured with enzymatic method; HDL cholesterol (mg/Dl) measured with homogeneous system method; LDL cholesterol (mg/dL) calculated method.

Additionally, by analysis of the potential interactions of other medications that could affect melatonin secretion such as beta-blockers and that may predispose to sleep insomnia such as lipid-lowering agents, some of the various pharmacological or non-pharmacological treatments used by patients according to the doses of melatonin were compared. The results were presented in Table 3. We did not find statistically significant differences between groups.

Table 3: Comparison of pharmacological or non-pharmacological treatments used in patients according to melatonin dose.

	Melatonin dose 40 to 79 mg/day N= 37		Melatonin dose 80 to 200 mg/day N= 43		
	n	%	n	%	*P*
Sleep-related drugs					
Benzodiazepines	14	17.5	16	20	0.65
Z drugs	8	10	15	18.8	0.25
Antidepressants	20	25	21	26.2	0.61

Antipsychotics	8	10	14	17.5	0.33
Pregabalin	7	8.8	4	5.0	0.31
Gabapentin	2	2.5	7	8.8	0.08
Drugs that can influence sleep					
Beta blockers	9	11.2	11	13,8	0.63
Hypolipidemics	12	15	8	10	0.16
Use of CPAP	12	15	16	20	0.56

4. DISCUSSION

This study was performed to examine several parameters in aged patients taking melatonin in doses equal to or greater than 40 mg/day for various sleep disorders. The population consisted mainly of women with an average age of 74 years. Most patients were under treatment for more than 4 years.

The main reason for indication was complaints of disorders in falling asleep and maintaining sleep (insomnia), the melatonin doses varying depending on the comorbidities clinically detected.

Laboratory variables related to liver function remain within the normal range after melatonin consumption regardless of the doses used. When analyzing the variables related to pharmacological treatments such as the use of benzodiazepines, antidepressants, hypnotics, antipsychotics, anticonvulsants, and antihypertension agents, we have not found any alterations related to melatonin doses either.

In clinical medicine, it has been debated anecdotally whether long-term high doses can negatively affect the body's production of melatonin, or it can cause individuals to become dependent over time (for a critical discussion see ref (22)). While it is a theoretical concern, there is a lack of significantly scientific evidence to support such a conclusion. In clinical applications, too much melatonin extended-release formats have been documented to produce side effects such as a “melatonin hangover” the next day, making it harder to fall asleep or get a good night's sleep for three or four hours and then wake up and not being able to fall asleep again (23).

Currently, the cytoprotective function of melatonin in older adults is proposed with more emphasis. It exerts important cellular protection against oxidative stress (4–8) Melatonin can flow freely through the selective blood-brain barrier, making it probably one of the most effective antioxidants in the central nervous system (15). Melatonin is active to increase glymphatic flow, helping to remove metabolic waste such as amyloid buildup (24, 25).

The strengths of the present research lie in that the findings provide valuable information about the use of fast release melatonin (free of other components, such as vitamins or minerals) in high doses, without significant alterations in the parameters analyzed. This information obtained can be used to develop future research, without fear of using high doses for therapeutic purposes, given that the doses of the over-the-counter drug remain insufficient, especially for older adults. We found no significant adverse effects or benefits related to the different subgroups according to melatonin dosages; additionally, the homogeneity of the sample constitutes a strength when conducting comparative analyses. Although the analyzed populations are different, our findings contrast with some previous publications that reported adverse effects, some severe, in pediatric patients (26).

Our study also had several limitations. It is a cross-sectional, retrospective analysis, so relevant data could be lost and it does not allow modifications to be made/added to the variables already established. Many studies have suggested a beneficial role for melatonin on total cholesterol as well as LDL or triglyceride levels (27, 28), effects not detected in the present sample. Perhaps this is due to the fact that the differences between conditions may be small, whereas the differences within conditions may be large in the control group. Assessment of the therapeutic response was subjective and based solely on parameters provided by the patients, such as that they appreciated their sleep was less fragmented and that falling asleep was faster, in addition to the request for prescriptions to continue with the treatment every 4 months because they appreciated that they were sleeping more efficiently than before. Likewise, gender representation was unbalanced as women were overrepresented in the sample. Female is associated with higher rates of poor sleep quality and insomnia in epidemiological studies, so sampling bias may increase the total number of these disorders in this study.

In conclusion, the usefulness of high doses of melatonin as an antioxidant and not only as a regulator of the circadian rhythm or insomnia must be stressed (29).

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AUTHORSHIP

Conceptualization, S.M.V. and D.P.C; data acquisition, S.M.V. and V.A.V; data analysis/interpretation, A.L.F and S.M.V; writing—original draft preparation, D.P.C, S.M.V., V.A.V., A.L.F., and A.G.C.; writing—review and editing, S.M.V., D.P.C., A.L.F and V.A.V.

CONFLICT OF INTERESTS

The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article**.**

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