Melatonin 4 mg as prophylactic therapy for primary headaches: a pilot study

Anastasia Bougea, MD, PhD[a]
Nikolaos Spantideas, PhD[b]
Vasilis Lyras, MD[c]
Theodoros Avramidis, MD, PhD[c]
Thomas Thomaidis, MD, PhD[c]

[a] 1st Department of Neurology, University of Athens Medical School, Aeginition Hospital, Athens, Greece
[b] SLT, Athens Speech and Language Institute, Athens, Greece
[c] Headache Clinic of Korgialenio – Benakio Red Cross Hospital, Athens, Greece

Correspondence to: Anastasia Bougea
E-mail: annita139@yahoo.gr

Summary

There is growing evidence that headaches are connected to melatonin secretion. Our aim was to assess the potential effectiveness of melatonin for primary headache prevention.
Forty-nine patients (37 with migraine and 12 with chronic tension-type headache, TTH) were prescribed oral melatonin, 4 mg, 30 minutes before bedtime for six months. Forty-one (83.6%) of the 49 patients completed the study, while eight dropped out for personal reasons.
A statistically significant reduction in headache frequency was found between baseline and final follow-up after six months of treatment (p=0.033 for TTH patients and p<0.001 for migraineurs). The Headache Impact Test score was significantly reduced in both groups of headache patients (p=0.002 and p<0.001, respectively).
At baseline, melatonin levels, measured both during a headache attack and a pain-free period, did not differ between patients with TTH and migraineurs (p=0.539 and p=0.693, respectively), and no statistically significant differences in Hamilton Depression Rating Scale scores were found between the two groups.
This pilot study shows promising results, in terms of headache frequency reduction and daily quality of life improvement, in both groups.

KEY WORDS: Hamilton Depression Rating Scale, Headache Impact Test (HIT-6), melatonin, primary headaches, prevention

Introduction

All organisms depend on the maintenance of a state of dynamic equilibrium or homeostasis, which is threatened by intrinsic and environmental stimuli. Environmental triggers have always been at the forefront of headache research. Since the pineal gland is considered to be a transducer of environmental stimuli into the neuroendocrine system, a pineal gland abnormality may be involved in headache etiology and homeostasis disruption. Levels of the pineal hormone melatonin have been found to be low in migraine (Claustrat et al., 1989; Murialdo et al., 1994; Brun et al., 1995) and in cluster headache (Leone et al.,1995). Melatonin can act as a chronobiotic (being a circadian pacemaker of sleep) (Cajochen et al., 2003), an antioxidant, an antihypertensive, an anxiolytic and a sedative (Yousaf et al., 2010). Experimental studies have indicated a dose-dependent analgesic effect of melatonin in animals (Pang et al., 2001; Naguib et al., 2003; Noseda et al., 2004; Tu et al., 2004; Mantovani et al., 2006; Wang et al., 2006). Oral melatonin has shown promising results in migraine prevention (3 mg, 30 minutes before bedtime) (Peres et al., 2004) and in cluster headache prophylaxis (10 mg) (Leone et al., 1996). The current study evaluates whether melatonin 4 mg has a beneficial effect as prophylactic therapy in tension-type headache (TTH) and migraine (the most disabling forms of headache), and whether it can play a role in the improvement of daily quality of life.

Materials and methods

Study population

The study population comprised subjects of both genders, aged 18-75 years, affected by primary headache (migraine or TTH) fulfilling the diagnostic criteria of the latest International Headache Society (IHS) headache classification (Headache Classification Committee of

the International Headache Society, 2013). The main exclusion criteria were secondary headaches and severe psychiatric and sleep disorders. Informed consent was obtained from all the patients. The study was approved by the local ethics committee. The procedures followed were in accordance with the ethical standards of the Helsinki Declaration of 1975, as revised in 1983.

Study design

The study was conducted at the outpatient Headache Clinic of Athens Korgialenio Benakio Hospital from January 2010 to June 2012. The recruited patients were classified in two groups: i) migraine with and without aura present for at least three months with at least four migraine attacks per month; ii) TTH, with over 15 headache days per month for at least three months. Patients on systemic prophylactic therapy were instructed to continue this therapy throughout the duration of the trial and, during attacks, to take (as needed) the symptomatic therapy they usually used as rescue therapy. A detailed headache history was obtained from all the patients. Physical, neurological and ophthalmological examinations were conducted and, when indicated, specific neuroimaging (MRI) investigations were performed.

The study period for every patient was six months. The scheduled visits were one initial (baseline) visit and two follow-up visits: at two and six months after initiation of melatonin prophylaxis.

At the baseline visit, the diagnosis was confirmed and a clinical and neurological examination was performed. Blood samples, for measurement of melatonin levels, were taken both during a headache attack and during a pain-free period. Both blood samples were taken at the same time of day (11 p.m.) under low light to avoid bias due to the normal circadian fluctuation of melatonin levels in blood. Blood was collected into a heparinized tube and immediately centrifuged at 4°C, 2000 g for 20 minutes; plasma was decanted and stored at –20°C until the radioimmunoassay test was performed (Graham et al., 1998). To allow us to identify, at the beginning of the study, any differences between these two main primary headaches, all patients completed the Hamilton Depression Rating Scale (HAMD), the Epworth Sleepiness Scale (ESS) and the Headache Impact Test (HIT-6). As mentioned, any current prophylactic headache therapy was continued and all patients were instructed to record the duration and frequency of their headache attacks in diaries. After completion of the baseline assessment, the subjects included in the study started melatonin prophylactic therapy consisting of 4 mg/day of melatonin (Circadin®, a prolonged release melatonin formulation) administered orally, 30 minutes before bedtime.

Visit 2 took place eight weeks after initiation of melatonin prophylactic therapy and comprised an interview with the patient during which progress with the prophylactic therapy was discussed and the headache diaries were reviewed. Possible side effects of the melatonin treatment were also recorded.

At visit 3 (final visit), six months after the initiation of the melatonin prophylaxis, all headache diaries were collected and HIT-6 was repeated. Visit 3 marked the official end of the study, and the patients were informed of this, but the melatonin prophylactic treatment was continued. Patients had to have adhered to the treatment for at least six months to be included in the analysis of the data.

The HIT-6 is a self-administered, six-item questionnaire that measures the impact of headache in several domains: social functioning, role functioning, vitality, cognitive functioning and psychological distress. Each question is presented as a five-point Likert item measured on a scale anchored at never (6) and always (13). The results of the six items were summed to give the total score, which thus ranged from 36 to 78. The impact of headache, according to HIT-6 scores, was graded as follows: a score ≤49 describes little or no impact; 50–55, some impact; 56–59, substantial impact; and ≥60 severe impact. A score >56 was considered clinically significant. The HIT-6 shows good internal consistency (0.89) and test-retest reliability (0.90), construct validity and responsiveness in general headache patients (Kosinski et al., 2003).

The HAMD is a 17-item scale that evaluates depressed mood, vegetative and cognitive symptoms of depression, and co-morbid anxiety symptoms. It provides ratings on current DSM-IV symptoms of depression, with the exception of hypersomnia, increased appetite and impaired concentration/indecision. The 17 items are rated on either a five-point (0–4) or a three-point (0–2) scale. The five-point scale items use the following ratings: 0 = absent; 1 = doubtful to mild; 2 = mild to moderate; 3 = moderate to severe; 4 = very severe. A rating of 4 is usually reserved for extreme symptoms. The three-point scale items use the following ratings: 0 = absent; 1 = probable or mild; 2 = definite. Applying the established clinical cut-offs, HAMD scores are classified in three groups (absent, mild and definite depression) (Zimmerman et al., 2013).

The ESS (Johns, 1991) is a brief self-administered questionnaire that measures average daytime sleepiness. Patients rate their probability of falling asleep on a scale from 0 to 3 for eight different situations. The scores for the eight questions are added together to obtain a single total (a number between 0 and 24). A number in the 0–9 range is considered to be normal while a number in the 10–24 range indicates excessive sleepiness. The internal consistency reliability of the test ranges from 0.74 to 0.88.

Statistical analysis

Continuous variables are expressed as mean and standard deviation (SD). Quantitative variables are expressed as absolute and relative frequencies. For the comparison of proportions, Fisher's exact tests were used. For the comparison of quantitative study

factors between the TTH and migraine group, the non-parametric Mann-Whitney test was computed for non-normal variables. Changes in attack frequency and HIT-6 scores during the follow-up period in the two groups (TTH and migraine) were evaluated using the Wilcoxon signed-rank test. The Spearman correlation coefficient was used to explore the association of two continuous variables. All p values reported are two-tailed. Statistical significance was set at 0.05 and analyses were conducted using SPSS statistical software (version 19.0).

Results

A total of 49 patients (12 TTH, 37 migraine) met the inclusion criteria and were included in this study. Forty-one (83.6%) of the 49 patients completed the study, while eight dropped out for personal reasons. The baseline characteristics of the 49 participants are described in table I.

As shown in table II which shows the results of the intervention, oral melatonin 4 mg had a favorable effect on attack frequency, which was found to be reduced in both the migraine and the TTH patients after six months of prophylactic therapy. No patient reported an increase in headache frequency.

The HIT-6 score (Table II) was statistically significantly reduced in the migraineurs after the treatment ($p<0.001$). A significant benefit of melatonin on headache impact was also recorded in the TTH group ($p=0.002$) at the end of the study period.

The main secondary outcome, melatonin levels measured both during a pain-free period and during a headache attack, did not show any statistically significant differences between the migraine and TTH patients ($p=0.693$ and $p=0.539$ respectively, mean values are shown in table I) or between males and

Table I - Demographic and baseline characteristics of the total study population.

	TTH n=12	Migraine n=37	p-value[1]
Sex			
Male	4 (33.3%)	7 (18.9%)	0.427
Female	8 (66.7%)	30 (81.1%)	
Age, years (mean ± SD)	45.25 ± 10.25	38.65 ± 11.77	0.012**
Duration of headache attacks, hours (mean ± SD)	13.25 ± 12.22	11.86 ± 8.90	0.852**
Drug therapy for headache attacks			
NSAIDs	9 (75%)	29 (78.4%)	0.743*
NSAIDS+triptans	1 (8.3%)	6 (16.2%)	
NSAIDS+antidepressants	1 (8.3%)	0 (0)	
NSAIDs+anxiolytics	1 (8.3%)	1 (2.7%)	
Triptan	0	1 (2.7%)	
Mean duration of prophylactic drug therapy before inclusion in the study, months (mean ± SD)	4.75 ± 2.05	4.24 ± 2.41	0.461**
Mean ESS score ± SD	4.41 ± 2.71	3.87 ± 2.92	0.249**
Hamilton Depression Rating Scale			
Absent (0–7)	7 (58.3%)	26 (70.27%)	0.098*
Mild (8–10)	2 (16.7%)	10 (27.02%)	
Definite (>10)	3 (25%)	1 (2.71%)	
Mean Mel Inter(pg/ml), mean ± SD	11.05 ± 7.46	10.58 ± 4.5	0.693**
Mean Mel Attack(pg/ml), mean ± SD	7.61 ± 4.3	6.65 ± 3.83	0.539**

Abbreviations: TTH=tension-type headache, NSAIDs=nonsteroidal anti-inflammatory drugs; Mel Inter=melatonin level during a pain-free period; Mel Attack=melatonin level during headache attack; ESS=Epworth Sleepiness Scale.
[1] Difference of frequencies tested with Pearson's chi-square, difference of means with Student's t-test and non-parametric Mann-Whitney U applied in each type of headache. p significant at <0.05; *Fisher's exact test; ** Mann-Whitney test.

Table II - Outcomes in melatonin intervention period compared to baseline.

Type of headache	AF Baseline mean±SD	AF 6 months mean±SD	p-value[1]	HIT-6 Baseline mean±SD	HIT-6 6 months mean±SD	p-value[1]
TTH	15.91 ± 6.88	5.33 ± 2.57	0.033	57.66 ± 8.42	36.7 ± 22.5	0.002
Migrane	4.72 ± 0.73	2.18 ± 0.84	<0.001	63.51 ± 5.43	44.37 ± 23.94	<0.001

Abbreviations: AF=attack frequency (mean per 4 weeks); TTH=tension-type headache; HIT=Headache Impact Test; SD=standard deviation. p significant at <0.05; [1]Wilcoxon signed rank test.

females (pain-free period mean±SD: 10.4±7.1 vs 10.7±4.7, p=0.853; headache attack mean±SD: 5.9±3.8 vs 7.1±3.9, p=0.351). In the total headache group, melatonin levels during headache attack were not significantly correlated with HAMD score (r=–0.11, p=0.465) or ESS score (r=0.10, p=0.475). The two headache groups showed no statistically significant difference in either HAMD (p=0.098) or ESS (p=0.249) scores at baseline.

Discussion

The results of this pilot study support our hypothesis that oral melatonin 4 mg has a positive role on headache frequency in patients suffering from TTH and migraine. In addition, the HIT-6 score was significantly reduced, indicating an improvement in daily quality of life, both in patients with migraine and in those with TTH. We also showed a non-significant relationship between melatonin levels and HAMD score during both headache attacks and pain-free periods.

There are certain limitations in our study that could be improved in future studies. The main ones are the open-label design and the lack of a control group. Another issue to address is the size of the sample, and especially the small number of patients with TTH. Crossover studies with established headache prophylactic therapeutic agents would require a longer follow-up period in order to determine whether melatonin works as prophylactic therapy when used in the long term, but crossover trials are vulnerable to the effects of subject withdrawal. The eight withdrawals in our study probably did not have a major impact on its results. In addition, our findings are limited by the lack of pre- vs post-intervention comparisons of HAMD and ESS scores. These two scales, used simply for the purpose of detecting possible differences between the two groups of headache patients at baseline, were administered only in the initial phase. That said, this trial was not primarily designed to assess the quality of sleep as the majority of subjects did not have insomnia.

Two double-blind placebo-controlled studies have documented a significant effect of melatonin on sleep quality and morning alertness in patients with insomnia (Lyseng-Williamson, 2012). In a randomized, double-blind, placebo-controlled trial, sleep quality assessed using the Pittsburgh Sleep Quality Index did not improve during melatonin treatment in migraineurs (Alstadhaug et al., 2010).

Serum melatonin levels are reduced in patients with cluster headache, particularly during a cluster period (Pringsheim et al., 2002). As regards plasma melatonin levels in migraine, the limited published data available derive from three small studies, the results of which suggested that female migraine sufferers have decreased nocturnal plasma melatonin levels both overall and during migraine attacks (Claustrat et al., 1989; Brun et al., 1995; Murialdo et al., 1994). Our study was not able to confirm these findings as we did not include a control group. Abnormal melatonin levels could reflect a global sympathetic hypofunction. Furthermore, migraine sufferers without depression had lower nocturnal plasma melatonin levels than controls, and migraine patients with superimposed depression exhibited the greatest deficiency of melatonin compared with the control group (Claustrat et al., 1989).

Similarly, there is little published literature on melatonin treatment in other primary headaches and, accordingly, only a few studies with small numbers of participants have reported benefits of melatonin treatment in primary headaches. A double-blind, placebo-controlled study of 20 patients showed the efficacy of oral melatonin 10 mg for cluster headache prophylaxis (Pringsheim et al., 2002). In an open-label trial conducted in 34 patients, melatonin 3 mg reduced headache frequency and intensity (Peres et al., 2004). Another study (Alstadhaug et al., 2010) provided Class I evidence that 2 mg of prolonged release melatonin given one hour before bedtime failed to replicate the results of the above-mentioned open-label study with 3 mg of oral melatonin. It can be hypothesized that the benefit of melatonin in migraine sufferers is dose dependent, but the authors of these studies stated that the dose of melatonin was appropriate, and they actually suggest that lower doses have a greater phase-shifting effect (Peres et al., 2004; Alstadhaug et al., 2010). Therefore, no clear relation exists between physiological melatonin levels and its pharmacological doses. Neither of the above studies assessed the effect of melatonin treatment on quality of life or depression symptoms.

Although it was not statistically significant, this is the first study showing a trend toward higher melatonin levels and decreased HAMD score during headache attacks, which suggests an antidepressive effect of melatonin. In accordance with the present results, previous studies have also found no toxicological effect that could compromise the use of melatonin.

References

Alstadhaug KB, Odeh F, Salvesen R, et al (2010). Prophylaxis of migraine with melatonin: a randomized controlled trial. Neurology 26;75:1527-1532.

Brun J, Claustrat B, Saddier P, et al (1995). Nocturnal melatonin excretion is decreased in patients with migraine without aura attacks associated with menses. Cephalalgia 15:136-139.

Cajochen C, Kräuchi K, Wirz-Justice A (2003). Role of melatonin in the regulation of human circadian rhythms and sleep. J Neuroendocrinol 15:432-437.

Claustrat B, Loisy C, Brun J, et al (1989). Nocturnal plasma melatonin levels in migraine: a preliminary report. Headache 29:242-245.

Graham C, Cook MR, Kavet R, et al (1998). Prediction of nocturnal plasma melatonin from morning urinary measures. J Pineal Res 24:230-238.

Headache Classification Committee of the International Headache Society (IHS) (2013). The International Classification of Headache Disorders, 3rd edition (beta version), Cephalalgia 33:629-808.

Johns MW (1991). A new method for measuring daytime sleepiness: the Epworth sleepiness scale. Sleep 14:540-545.

Kosinski M, Bayliss MS, Bjorner JB, et al (2003). A six-item short-form survey for measuring headache impact: the HIT-6. Qual Life Res 12:963-974.

Leone M, Lucini V, D'Amico D, et al (1995). Twenty-four-hour melatonin and cortisol plasma levels in relation to timing of cluster headache. Cephalalgia 15:224-229.

Leone M, D'Amico D, Moschiano F, et al (1996). Melatonin versus placebo in the prophylaxis of cluster headache: a double-blind pilot study with parallel groups. Cephalalgia 16: 494-496.

Lyseng-Williamson KA (2012). Melatonin prolonged release: in the treatment of insomnia in patients aged ≥55 years. Drugs Aging 29:911-923.

Mantovani M, Kaster MP, Pertile R, et al (2006). Mechanisms involved in the antinociception caused by melatonin in mice. J Pineal Res 41:382-389.

Murialdo G, Fonzi S, Costelli P, et al (1994). Urinary melatonin excretion throughout the ovarian cycle in menstrually related migraine. Cephalalgia 14:205-209.

Naguib M, Hammond DL, Schmid PG 3rd, et al (2003). Pharmacological effects of intravenous melatonin: comparative studies with thiopental and propofol. Br J Anaesth 90:504-507.

Noseda R, Hernández A, Valladares L, et al (2004). Melatonin-induced inhibition of spinal cord synaptic potentiation in rats is MT2 receptor dependent. Neurosci Lett 360:41-44.

Pang CS, Tsang SF, Yang JC (2001). Effects of melatonin, morphine and diazepam on formalin-induced nociception in mice. Life Sci 68:943-951.

Peres MF, Zukerman E, da Cunha Tanuri F, et al (2004). Melatonin, 3 mg, is effective for migraine prevention. Neurology 63:757.

Pringsheim T, Magnoux E, Dobson CF, et al (2002). Melatonin as adjunctive therapy in the prophylaxis of cluster headache: a pilot study. Headache 42:787-792

Tu Y, Sun RQ, Willis WD (2004). Effects of intrathecal injections of melatonin analogs on capsaicin-induced secondary mechanical allodynia and hyperalgesia in rats. Pain 109:340-350.

Yousaf F, Seet E, Venkatraghavan L, et al (2010). Efficacy and safety of melatonin as an anxiolytic and analgesic in the perioperative period: a qualitative systematic review of randomized trials. Anesthesiology 113:968-976.

Wang T, Li SR, Dai X, et al (2006). Effects of melatonin on orphanin FQ/nociceptin-induced hyperalgesia in mice. Brain Res 1085:43-48.

Zimmerman M, Martinez JH, Young D, et al (2013). Severity classification on the Hamilton Depression Rating Scale. J Affect Disord 150:384-388.