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Melatonin, 3 mg, is effective for migraine prevention

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There is increasing evidence that melatonin secretion and pineal function are related to headache disorders. Altered melatonin levels have been found in cluster headache, migraine with and without aura,[1] menstrual migraine,[2] and chronic migraine.[3]

A great variety of melatonin mechanisms may be linked to headache pathophysiology.[3] Melatonin may have anti-inflammatory effect, it scavenges toxic free radicals, reduces the up-regulation of proinflammatory cytokines, and inhibits nitric oxide synthase activity and dopamine release. It also interferes with membrane stabilization, γ-aminobutyric acid and opioid analgesia potentiation, protection from glutamate neurotoxicity, neurovascular regulation, and serotonin modulation. Melatonin and indomethacin share similar chemical structure.[4] Melatonin is then a possible candidate for migraine prevention. We tested the hypothesis of the potential effectiveness of melatonin for migraine prophylaxis.

Methods. We performed an open-label trial of melatonin, 3 mg, for migraine prevention. Forty patients with episodic migraine with or without aura according to the International Headache Society (IHS) diagnostic criteria were screened for the baseline period. Three patients did not have headaches during the baseline period; three patients were lost to follow-up evaluation. Thirty-four patients (29 women, 5 men) started prophylactic treatment with melatonin, 3 mg, 30 minutes before bedtime. Thirty-two patients completed the study. All patients signed an informed consent form. The local and federal ethics committees approved the study.

Study participants experienced between two and eight migraine attacks per month. Chronic daily headache patients were excluded. Patients on preventive therapy 3 months before recruitment for the trial were excluded. Patients were examined, and an adequate headache history was ascertained. Patients with insomnia or considerable sleep hygiene problems were excluded. The total study length was 4 months, with a 1-month baseline period and 3-month therapy phase. A study diary was provided to each study participant.

The primary endpoint was the percentage of patients with >50% reduction in headache frequency comparing baseline vs month 3 after treatment. Headache intensity, duration, and analgesic consumption were also ascertained. Analgesic units were considered according to the IHS classification. Triptans, ergots, nonsteroidal anti-inflammatory drugs, and analgesics were taken. An intention-to-treat analysis was done; all patients who returned for at least one follow-up visit were included (34 patients); and the mean values were carried to month 3.

One-way repeated-measures analysis of variance was used to compare values between the four periods. Tukey method was used for post hoc pairwise comparisons. All p values reported were two-tailed, and values <0.05 were considered significant.

Results. Thirty-two of 34 patients completed the study; 78.1% of patients (25/32) who completed the study had at least 50% reduction. No patients reported increase in headaches. Complete (100%) response was achieved in 8 patients (25%), >75% reduction was found in 7 patients (21.8%), and 50 to 75% reduction was seen in 10 patients (31.3%) after 3 months of therapy. Melatonin decreased headache frequency (7.6 ± 3.2 headaches/month at baseline, 4.4 ± 2.5 at month 1, and 3.0 ± 3.1 at month 3; $p < 0.001$), headache intensity on a 0 to 10 scale (7.4 ± 1.3 at baseline, 5.5 ± 1.9 at month 1, and 3.6 ± 2.7 at month 3; $p < 0.001$), and duration in hours (19.8 ± 19.8 at baseline, 10.2 ± 13.4 at month 1, and 8.8 ± 12.4 at month 3; $p < 0.001$). Significant clinical improvement was already achieved at month 1. Overall analgesic and triptan consumption also decreased ($p < 0.001$). Menstrually associated migraines equally decreased in frequency. Two patients withdrew from the study, one because of excessive sleepiness and the other because of alopecia. Three patients spontaneously reported increase in libido. No changes in body weight occurred (baseline 62.5 ± 10.0 kg vs month 3 62.5 ± 10.2 kg).

Discussion. Melatonin and migraine are linked in several ways. A circadian attack predilection has been reported in episodic (55%) and chronic (62.5%) migraineurs.[5] A distribution of attacks according to the estrous cycle is evident in menstrual migraine. True menstrual migraine occurs in 14%; menstrually associated migraine can occur in up to 55% of cases.[6] A circannual variation can be observed in cyclic migraine or in the cluster migraine association.

Only small studies reported benefit in migraine patients from melatonin treatment. One showed relief after melatonin infusion in status migrainous. A patient with delayed sleep phase syndrome and migraine had a dramatic decrease in headaches after beginning melatonin treatment.[7] This is the first study to assess melatonin efficacy in migraine prevention. In our small series of migraine patients, melatonin was effective in reducing the number of headache days per month. A controlled study may be worthwhile.

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