Migraine induced by melatonin withdrawal: a clue for future trials?

Jean-Marie Annoni[a], Stéphane Cook[b]
[a] Neurology, Department of Medicine, University and Hospital of Fribourg, Switzerland
[b] Cardiology, Department of Medicine, University and Hospital of Fribourg, Switzerland

Funding / potential competing interests: No financial support and no other potential conflict of interest relevant to this article was reported.

Summary

Background: Melatonin supplementation has been suggested as influencing migraine frequency, but the few published studies on this subject have arrived at differing conclusions.

Case: A 37-year-old white male, who had experienced four to six attacks of migraine with aura yearly over the previous nineteen years, noticed repeated morning migraine attacks with aura 24 to 48 hours after the intake of melatonin (patient's estimate of frequency was 80% of the events), which was being used as a sleep inducer at a dose of 3–6 mg. The intensity of pain was independent of duration and quality of sleep. Such attacks were considered to be provoked by the melatonin withdrawal.

Conclusion: This case illustrates the complexity of the relationship between melatonin and migraines, and suggests that the selection of certain migraine phenotypes and the manipulation of the melatonin doses could be of value in further studies.

Key words: headaches; migraine; melatonin; therapy; withdrawal

Introduction

Migraine attacks can be associated with the circadian cycle in certain patients. Since the pineal gland, through melatonin synthesis, allows synchronisation between the environment and internal biological events, melatonin supplementation has been suggested as influencing migraine attacks and even preventing them [1]. To date, however, there are only a few studies on the efficacy of melatonin supplementation on the incidence of migraines (table 1). Amongst these open studies, one found improvement of headaches in 80% of patients who took 3 mg of melatonin at night [2]. Similar results were found in children, but once again this was only an open study [3]. However, results from a recent controlled study which compared 2 mg of melatonin with a placebo taken at night pointed to a lack of efficacy [4], independent of the type of migraine. The authors suggest that the melatonin effect may be an indirect one, rather through sleep and mood improvement. Melatonin supplementation is not currently considered as an evidence-based migraine therapy, in accordance with local and international guidelines [5]. At this point, case reports may help to define the relationship between melatonin, sleep and migraines, and also to optimise future therapeutic studies. Some people might even react paradoxically to melatonin supplementation, developing migraines after melatonin intake [6].

Correspondence:
Professor Jean-Marie Annoni, MD
Head of Neurology
Department of Medicine, University of Fribourg
Fribourg Medical Centre
CH-1708 Fribourg
Switzerland
jean-marie.annoni@unifr.ch

Case report

In line with this concept, we report here the case of a 37-year-old white male, who had experienced four to six attacks of migraine with aura yearly over the previous nineteen years, and who noticed repeated morning migraine attacks with aura 24 to 48 hours after taking melatonin. He gave his full consent to this report, in line with the local ethic rules. His migraines usually started in the morning, with visual aura, followed by headaches lasting for six to ten hours in general. No distinct trigger had yet been isolated. Effective treatment included aspirin and paracetamol. Since 2004, he had been using 3–6 mg of over-the-counter melatonin with variable frequency, but with a mean of about two to four times per month as a sleep inducer. He noticed that almost every single melatonin intake (patient's estimate is 80%) was subsequently followed by a migraine attack, usually two days later (25–35 events per year). His symptoms were identical to his usual migraine, beginning gradually over a five-to-ten-minute period, with a visual aura consisting of scintillating scotoma, photophobia and hemianopia. The headache phase of the migraine attack usually began within 30 minutes of the end of the aura phase and was of lesser intensity. Migraine intensity seemed to be at least partly dose-dependent, since taking twice the dose or taking melatonin on two consecutive days increased the symptoms; likewise, lowering the dose reduced the intensity of the symptoms. In this particular case, the onset of the migraine did not seem related to the efficacy of melatonin on sleep and was not associated with periods of wakefulness. These migraines were treated effectively in the same way as for his "usual" migraines. Neurological evaluation and brain imaging were normal. Furthermore, between 2004 and 2010, the yearly frequency of the "spontaneous" attacks remained virtually unchanged (two to five per year).The patient stopped using these pills in December 2010 and did not suffer any migraine attacks until his last visit in July 2011.

Table 1 Summary of the three published melatonin studies on migraine. In the three studies, melatonin was given in the evening, around 30 minutes before going to bed.

Authors	Year	Trial	Daily dose	Duration/pts/age-class	Effect
Peres et al.	2004	open-labelled	3 mg	3 mo / 34 pts / adults	positive
Alstadhaug et al.	2010	randomised-controlled	2 mg	2 mo / 48 pts / adults	negative
Miano S et al.	2010	open-labelled	3 mg	3 mo / 22 pts / children	positive

Conclusion

In our case report, we conclude that migraine may be due either to wearing-off manifestations or to a "rebound side effect". On the one hand, this case report illustrates that the relationship between melatonin and migraines is complex. On the other hand, this case report reinforces the theory that melatonin plays a role in the pathogenicity of migraine, and that some subjects are sensitive to changes in melatonin level. A possible mechanism is the antioxidant role of melatonin, which decreases the free radicals in the myelin, thus protecting against myelin oedema and mechanistic pressure over the hyperalgesic axons which can culminate in migraine [7]. Moreover, urinary melatonin concentration is lower in subjects suffering from migraine than in controls [8], and there is a lower urinary concentration of melatonin metabolites (such as 6–sulphatoxymelatonin) during the acute phase of migraine; this suggests, at least in certain patients, a pathophysiological relationship between the migraine attack and lowered melatonin secretions. Since the half-life of melatonin is short (less than 60 min), we suggest that in our patients migraine attack could be associated, though secondary mechanisms, with the fall of melatonin secretion provoked by melatonin withdrawal. Given the rarity of such reported effects, it also suggests that only a few patients may develop it. Thus as melatonin sensitivity concerns only a minority of patients, doses of more than 3 mg may be required, at least in some patients. Dose-response investigations have already been suggested to test the analgesic effect of melatonin [9]. Restricting tests to migrainous patients with aura and/or younger patients, taking family clusters [10] into consideration, and manipulating doses (>2 mg/day) might help to demonstrate any such effect.

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