

Q&A 220.2

Is melatonin effective for preventing cluster headache?

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Background

Cluster headache (CH) is a primary headache syndrome, within the group of trigeminal autonomic cephalalgias (TAC). It consists of excruciating unilateral pain typically in and around the eye and temple region. There are two types of CH classified according to duration. Episodic Cluster Headache (ECH) is defined as bouts lasting from seven days up to one year, with breaks of one month or more between episodes. Chronic Cluster Headache (CCH) attacks occur for more than one year without remission, or with breaks lasting less than one month (1). About 80% - 90% of patients have ECH, with the remaining 10% - 20% experiencing CCH (2).

Neurological disorders including primary headaches have been linked to an alteration in chronobiology (3). CH tends to be seasonal, happening at the same time annually with peaks soon after the longest or shortest days of the year. Attacks may also occur at the same time each day and about two-thirds of patients suffer CH during sleep. It has therefore been suggested that CH may result from an inability to synchronise the internal clock to environmental light cues (4).

The management of CH is divided into acute and preventative treatment. Acute treatment is used to abort attacks. Future episodes are prevented with prophylactic medication. There are relatively few evidence-based guidelines for the treatment of CH (2). Early diagnosis and treatment are essential to improve the quality of life in these patients (1).

Answer

Rationale for melatonin use in cluster headache

Melatonin is a naturally occurring hormone produced by the pineal gland and is structurally related to serotonin. It is associated with the control of circadian rhythms and entrainment to the light-dark cycle. Physiologically, melatonin secretion increases soon after the onset of darkness, peaks at 2-4 am and diminishes during the second half of the night (5).

Studies have shown a decrease in nocturnal melatonin secretion in CH patients as well as lower melatonin levels during cluster periods compared with remissions. Given this and the circadian nature of many CH attacks, melatonin has been tried with the aim of opposing the reduced levels of nocturnal melatonin (1). However melatonin is not licensed for the prevention of CH (5).

Melatonin studies

Two small studies have investigated the role of melatonin in the prevention (prophylaxis) of cluster headaches (6,7). The first was a double-blind, parallel group study, where 20 cluster headache sufferers received melatonin or placebo during an episode. Two of the patients experienced CCH, the remaining 18 had ECH. An initial 7-day run-in period with no prophylactic medication, was followed by oral melatonin 10 mg in the evening or placebo for 14 days (n=10 in each group). The two CCH patients stayed on their prophylactic medication, so the melatonin was adjunctive therapy in these cases. A headache diary card was used to record frequency, intensity and duration of attacks plus analgesic consumption. Daily mean values were calculated for each parameter. Most patients used subcutaneous sumatriptan to abort attacks, which caused problems with interpreting their intensity and duration. Therefore

the effectiveness of two-weeks of melatonin therapy was evaluated by comparing mean headache frequency and mean consumption of analgesics only, with the mean daily values for the first week (7-day run-in period). Although no primary endpoint was stated, the mean daily values for each week within groups were analysed. The mean number of daily attacks was statistically significantly reduced in the melatonin group when compared to the run-in period (ANOVA, $p < 0.03$). However, within the placebo group there was no statistical difference from baseline. Although not statistically significant, there were also strong trends towards reduced analgesic consumption in the melatonin group (ANOVA, $p < 0.06$). Five patients responded in the melatonin group. They started improving after 3 days of treatment with no further attacks after day 5 and until the end of the 14-day study, when melatonin was discontinued. Despite both being in the melatonin group, neither of the two CCH patients responded (6). However this trial did not compare melatonin directly with placebo, but analysed changes in both groups from baseline, making conclusive results difficult to achieve (2).

Another, smaller study investigated the use of 2mg controlled release melatonin as adjunctive therapy in 9 patients with CH (6 chronic, 3 episodic.) All patients continued their usual prophylactic medication, which had previously only provided partial relief. Acute treatment of attacks was also allowed throughout the study. ECH patients received placebo for 1 month, then melatonin for 1 month as a single bedtime dose. Patients with CCH completed a baseline diary for 1 month, then received 1 month of melatonin treatment, followed by 1 month of placebo. The primary endpoint was the number of headaches per day. Secondary endpoints were mean daily average consumption of analgesics, and the percentage of headaches categorised as mild, moderate or severe. There was no significant difference for the average number of headaches per day. In addition there was no significant difference for the average daily analgesic consumption. Neither were there any trends suggesting reduction in intensity of cluster headaches with melatonin. However it is not stated whether comparisons were within groups or between groups making interpretation difficult. In this study both ECH and CCH patients uncontrolled on conventional medication, experienced no benefit from the addition of melatonin to their existing therapy (7). A review of this small study concluded that the dosage used was probably inadequate to demonstrate efficacy (2). The authors of the study itself felt that the dose of melatonin was appropriate, actually producing greater levels than those achieved physiologically. However they stated that the controlled release formulation may have been a factor in lack of response. This is despite the release profile mimicking endogenous secretion more closely than a 10mg regular release dose. They also mention that the timing of administration in patients with ECH i.e. one month after the start of the CH episode, may have been a factor in the lack of therapeutic benefit. Their hypothesis is that melatonin might only be successful if taken at the beginning of the cluster attack, when it possibly resets the dysfunction in circadian rhythm within the hypothalamus (7).

The 2011 European Federation of Neurological Societies (EFNS) guidelines on the treatment of cluster headache and other trigemino-autonomic cephalgias briefly comment on the above studies. They mention that 10mg of melatonin was effective in the first study, but in the second study with refractory cluster headache melatonin produced no additional efficacy. Melatonin is not recommended as first or second line prevention in cluster headache, but the guidelines conclude that melatonin may be useful in some patients (8).

The British Association for the Study of Headache (BASH) guidelines for the management of cluster headache also mention that the first study suggests potential benefit from melatonin, but consider it to be a "drug with uncertain efficacy" (9).

Summary

- ◆ Cluster headaches are classified as primary headaches within the group of trigeminal autonomic cephalalgias (TAC). They occur as either Episodic Cluster Headache (ECH) or Chronic Cluster Headache (CCH). The excruciating pain suffered during attacks causes a poor quality of life (1).
- ◆ CH tends to be seasonal. Attacks may also occur at the same time each day and about two-thirds of patients suffer CH during sleep (4).
- ◆ The naturally occurring hormone melatonin is associated with the control of circadian rhythms and entrainment to the light-dark cycle. Physiologically, melatonin secretion increases soon after the onset of darkness (5).
- ◆ Decreased nocturnal secretion and low levels of melatonin have occurred in CH (1).
- ◆ Oral melatonin has been tried with the aim of opposing these reduced nocturnal levels in CH patients (1).
- ◆ There is very limited published evidence available, as there are only two small published studies on the use of melatonin as prophylaxis in CH (6,7).
- ◆ Whilst melatonin is not recommended as first or second line prevention in cluster headache, a dose of 10mg at bedtime may be useful as prophylaxis in some patients with ECH based on one small study (8). It is possibly less effective for those with CCH (6).
- ◆ Melatonin is not licensed for the prevention of CH (5).

Limitations

This Medicines Q&A does not cover trigger factors for CH, or any abortive/acute treatment of CH, neither does it discuss any preventative treatments other than melatonin. For full details on acute and preventative treatment, please refer to the EFNS Guidelines on the treatment of cluster headache and other trigemino-autonomic cephalalgias (8). The various potential mechanisms of melatonin in headache pathophysiology are not discussed here (eg. anti-inflammatory effects) – please see Peres reference (3).

Only published studies investigating the use of melatonin for the prevention of cluster headache have been included in this Medicines Q&A. Case reports have been excluded.

References

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Search strategy

Embase (via NHS Evidence): exp cluster headache/ AND exp melatonin/

Medline (via NHS Evidence): exp cluster headache/ AND exp melatonin/

IDIS: "MELATONIN 92000018" and Disease(s): "MIGRAINE 346"

Micromedex: Drugdex evaluation: melatonin

NHS Evidence. Accessed via <https://www.evidence.nhs.uk/>

In-house database: MiDatabank

eMC. Accessed via www.emc.medicines.org.uk