Is melatonin effective for preventing cluster headache?

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Background

Cluster headache (CH) is a primary headache disorder, which is classified as a trigeminal autonomic cephalgia (1,2). It consists of severe headache attacks of sudden onset, which are strictly unilateral and occur typically in and around the eye and temple region (1,2). The pain experienced during a cluster attack is very severe and recurrent attacks lead to significant disabilities (3). Attacks usually last around 15 to 180 minutes (1,2).

Cluster headache can be further divided into two types based on the duration and frequency of episodes (1). Episodic Cluster Headache (ECH) is defined as attacks occurring in periods lasting anywhere from seven days up to one year, separated by pain-free remission periods lasting at least 3 months (2). Chronic Cluster Headache (CCH) attacks occur for more than one year without remission, or with breaks lasting less than 3 months; about 10–15% of patients have chronic cluster headache.

The pathophysiology of cluster headache is not fully understood, but current theories implicate mechanisms such as vascular dilation and circadian effects (1).

Neurological disorders including primary headaches have been linked to an alteration in chronobiology (4). CH tends to be seasonal, happening at the same time each year 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 (5).

The treatment of cluster headache is primarily pharmacological and can be divided into acute, transitional and prophylactic treatment. Prophylactic therapy is perhaps the most important component of management and aims to reduce the frequency, severity and duration of attacks (3,6). Early diagnosis and treatment are essential to improve the quality of life in these patients (7).

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 (synchronisation) 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 (8).

Studies have shown a decrease in nocturnal melatonin secretion in CH patients as well as lower nocturnal melatonin levels during cluster periods compared with remissions (4). Given this and the circadian nature of many CH attacks, melatonin has been tried with the aim of reducing cluster headache attacks (7). Melatonin is not licensed for the prevention of CH (8).

Melatonin studies

Two small studies have investigated the role of melatonin in the prevention of cluster headaches (9,10).
Leone et al (1996)
This double-blind, parallel group study randomised 20 cluster headache sufferers (2 chronic, 18 episodic), after a 7 day run-in period with no medication, to melatonin 10mg in the evening or placebo for 14 days during a cluster episode (9). The effectiveness of melatonin was evaluated by comparing headache frequency and the consumption of symptomatic drugs with abolition of the headache. Compared to the run-in period, there was a reduction in the mean number of daily attacks in the melatonin treated group (p<0.03), but not in the placebo group (p=0.7). Although not statistically significant, there was also a trend towards reduced analgesic consumption in the melatonin group (p<0.06). Five patients responded in the melatonin group and five did not. Responders started improving after 3 days of treatment with no further attacks after day 5 and until the end of the 14-day study. No patients complained of adverse effects. This trial did not compare melatonin directly with placebo, but analysed changes in both groups from baseline (11). This, along with the small number of trial subjects, makes conclusive results difficult to achieve.

This single-blinded study investigated the use of 2mg controlled release melatonin once daily at bedtime versus placebo as adjunctive therapy in 9 patients with CH (6 chronic, 3 episodic) (10). ECH patients received placebo for 1 month, then melatonin for 1 month. 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 consumption of analgesics, and the percentage of headaches categorised as mild, moderate or severe. For all CH patients there was no significant difference in the average number of headaches per day for melatonin and placebo. In addition there was no significant difference for the average daily analgesic consumption, and no trends suggesting reduction in intensity of cluster headaches with melatonin.

A review of this second study concluded that the dosage used was probably inadequate to demonstrate efficacy (11). However the authors of the study itself felt the dose of melatonin was appropriate, producing greater levels than those achieved physiologically, but they stated that the controlled release formulation may have been a factor in lack of response (10). This is despite the release profile mimicking endogenous secretion more closely than a 10mg regular release dose. They also mentioned 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, hypothesising that melatonin might only be successful in ECH if taken at the beginning of the cluster attack.

It appears that many issues related to dose, tablet formulations and timing of administration need to be resolved with regard to testing melatonin therapy (6).

Guidelines
The 2012 full NICE clinical guidelines on the diagnosis and management of headaches in adults and young people discuss the Leone et al study, but state that the evidence this trial provides is of very low quality (3). The guidelines also state that there is too much uncertainty to determine whether there is a difference between melatonin and placebo in reducing headache frequency or reducing the number of analgesics consumed per day in people with cluster headaches.

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 (12). They mention that melatonin was effective in the first study, but in the second study it produced no additional efficacy. Melatonin is not recommended as first or second line prevention in cluster headache, but the guidelines suggest that melatonin “is useful in some patients”.

The British Association for the Study of Headache (BASH) guidelines for the management of cluster headaches discuss the studies of Leone et al and Pringsheim et al, but do not make any recommendations for the use of melatonin in the treatment of cluster headache.
headache also mention that the first study suggests potential benefit from melatonin, but consider it to be a drug with “uncertain efficacy” (13).

American Headache Society guidelines updated in 2016 state that there are no new data from randomised controlled trials that contribute to determining the efficacy and safety of a number of preventive treatments for CH, including melatonin. The guidelines classify melatonin as “possibly effective” (14).

Other
A systematic review (2018) to assess the efficacy and safety of melatonin for primary headache did not identify any further RCTs to Leone et al investigating melatonin in CH. The authors concluded there was insufficient evidence to support use of melatonin in clinical practice for preventing primary headache (15).

Summary

- Cluster headache (CH) is a primary headache disorder, which is classified as a trigeminal autonomic cephalgia. The pain experienced during a cluster attack is very severe and recurrent attacks lead to significant disabilities.
- 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.
- Decreased nocturnal secretion and low levels of melatonin have occurred in CH.
- Oral melatonin has been tried with the aim of reducing cluster headache attacks.
- There is very limited published evidence available, with only two small published studies on the use of melatonin as prophylaxis in CH, only one of which demonstrated efficacy of melatonin in reducing number of attacks.
- The NICE clinical guideline on the diagnosis and management of headaches states there is too much uncertainty to determine whether there is a difference between melatonin and placebo in reducing headache frequency in people with CH.
- European Federation of Neurological Societies (EFNS) guidelines on the treatment of cluster headache state that, whilst melatonin is not recommended as first or second line prevention in cluster headache, it may be useful as prophylaxis in some patients based on one small study.
- It appears that many issues related to dose, tablet formulations and timing of administration need to be resolved with regard to testing melatonin therapy.
- Melatonin is not licensed for the prevention of CH.

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. Consult alternative reference sources for further details on acute and preventative treatment. The various potential mechanisms of melatonin in headache pathophysiology are not discussed here. 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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Quality Assurance

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