A Cluster Headache Responsive to Ramelteon, a Selective Melatonin MT$_1$/MT$_2$ Receptor Agonist

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Abstract

Patients with cluster headaches occasionally fail to respond to conventional preventive treatments. We herein report a case of a patient with a cluster headache in which the symptoms were refractory to conventional preventive treatments except for high-dose glucocorticoids. The headache attacks occurred daily while sleeping, thus the patient suffered from insomnia. Ramelteon, a selective melatonin receptor agonist and a member of a new class of insomnia therapies, completely suppressed the attacks during sleep and provided rapid relief from insomnia. This is the first English case report to describe the efficacy of ramelteon as a preventive treatment for cluster headaches.

Key words: cluster headache, ramelteon, melatonin, preventive treatment

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Introduction

A cluster headache is the most painful form of primary headache and it is characterized by strictly unilateral pain localized in or around the eye accompanied by ipsilateral autonomic features. Another characteristic feature of a cluster headache is the circadian rhythmicity of the attacks, which can last from 15-180 minutes if left untreated (1, 2). The diagnostic criteria for cluster headaches were established by the International Headache Society (3). During the worst attacks, the intensity of pain is excruciating, and patients are usually unable to lie down and characteristically pace around (4-6).

Treatments for a cluster headache can be divided into acute therapy aimed at stopping individual attacks and prophylactic therapy aimed at preventing recurrent attacks during the cluster period (7). The first-line treatment options for acute cluster headache attacks are a subcutaneous injection of sumatriptan and 100% oxygen (7). Verapamil is the first option for episodic cluster headache prophylaxis (7). Due to the relatively long time required for a response to verapamil, glucocorticoids are used as adjunctive therapy (7). Patients with cluster headaches occasionally fail to respond to conventional preventive treatments.

Ramelteon is a selective MT$_1$/MT$_2$ receptor agonist and is the first drug in a new class of insomnia therapies (9). We herein report the case of a patient whose cluster headache improved following treatment with ramelteon. To the best of our knowledge, no previous English reports have described the use of ramelteon to treat a cluster headache.

Case Report

The patient was a 41-year-old man who visited our headache clinic with a 20-year history of left-sided excruciatingly severe stabbing pain located in his orbit. The attacks were associated with a nasal obstruction, conjunctival injection, restlessness, and migrainous features such as nausea, vomiting, and phonophobia. No continuous background pain was identified. The duration of the attacks was approximately 60 minutes, with a frequency of two to three attacks per 24 hours. The attacks primarily occurred during sleep. He had previously been treated with subcutaneous sumatriptan
tan (3 mg), oral sumatriptan (50 mg), oral eletriptan (20 mg), verapamil (maximum of 240 mg/day), oral prednisone (maximum of 30 mg/day), lithium (maximum of 400 mg/day), topiramate (maximum of 100 mg/day), and valproic acid (maximum of 200 mg/day). He had responded to only subcutaneous sumatriptan. His medical and family history was otherwise unremarkable. He was not on any medications and used no drugs. His vital signs, physical examination, and neurological examination were normal. Laboratory testing was also normal. His symptoms fulfilled the International Classification of Headache Disorders 3 beta criteria for a cluster headache.

He was initially treated with subcutaneous sumatriptan (3 mg) and topiramate (maximum of 200 mg/day). The attacks completely ceased with subcutaneous sumatriptan once they had begun, however, the frequency of the attacks did not decrease. Verapamil (maximum of 360 mg/day) was given as an alternative to topiramate, but also failed to suppress the attacks. After a single intravenous administration of methylprednisolone (1,000 mg), the patient was treated with oral prednisone (60 mg per day) for 5 consecutive days, with tapering during the 5-day administration period. The attacks completely ceased with intravenous methylprednisolone for 2 days, and then the frequency of the attacks decreased to once or twice a day. As the attacks occurred during sleep, ramelteon was started at a dosage of 8 mg at bedtime while maintaining the administration of verapamil; no intravenous administration of methylprednisolone or oral prednisone was given. The attacks during sleep completely ceased with ramelteon administration once they had begun, however, the attacks occurred early in the morning. The number of headache attacks decreased from approximately 10 times a week to two or three times a week. The intensity of the headache and response to subcutaneous sumatriptan did not differ compared to before the administration of ramelteon. The patient experienced no adverse effects associated with the ramelteon treatment. The cluster period ended 6 weeks after treatment with ramelteon.

Discussion

Arai reported the first therapeutic benefit of ramelteon for a cluster headache in 2013 written in Japanese (10). He reported the case of a 31-year-old male doctor with a 5-year history of left-sided excruciatingly severe stabbing pain located in his orbit. The attacks were associated with a nasal obstruction, conjunctival injection, and rhinorrhea. The duration of the attacks was approximately 2 hours, and they occurred 2 hours after going to bed. When the patient took 8 mg ramelteon at bedtime, he was able to sleep until morning without headache attacks.

The posterior hypothalamic region plays an important role in the pathophysiology of a cluster headache (11). A fall in the nocturnal plasma melatonin level occurs in patients with cluster headaches, suggesting that melatonin may play a role in the promotion of attacks (8, 12). Neuroimaging studies have confirmed clinical and neuroendocrinological data indicating hypothalamic involvement in a cluster headache (11). A positron emission tomography study demonstrated that the ipsilateral posterior hypothalamus is activated during cluster headache attacks (13). Furthermore, a voxel-based morphometry study demonstrated a high cell density in the ipsilateral posterior hypothalamus gray matter (14). Additionally, proton magnetic resonance spectroscopy studies have shown decreased ratios of N-acetyl aspartate to creatine-phosphocreatine and decreased ratios of choline to creatine-phosphocreatine in the hypothalamus of patients with cluster headaches (15).

As a fall in the nocturnal plasma melatonin level occurs in patients with cluster headaches, Leone et al. studied the efficacy of melatonin for cluster headaches. In a double-blinded, placebo-controlled study of 20 patients with cluster headaches, patients receiving 10 mg oral melatonin a day experienced a significant reduction in the headache frequency (p<0.03), and no side effects occurred in either group (8).

Ramelteon, which is a highly selective agonist for the melatonin MT1/MT2 receptors that are believed to mediate the circadian rhythm in mammals, is used to treat insomnia (9). Ramelteon has negligible affinity for MT1 binding sites and other receptors in the brain, including opiate, dopamine, benzodiazepine, and serotonin receptors, which may explain the lack of significant adverse events and lack of abuse or dependence potential observed with ramelteon (9). In three clinical trials in patients with chronic insomnia, 8 mg ramelteon was effective in reducing sleep latency and not associated with any significant or clinically relevant residual effects (9). The mean half-life of 8 mg ramelteon is longer than that of melatonin (1.4 h vs. 30-50 min) (8, 9). Following oral administration, ramelteon undergoes extensive first-pass hepatic metabolism. The half-life of the main metabolites, one of which is 20- to 100-fold more active than melatonin, ranges from 1 to 3 hours (9). In our patient, ramelteon did not completely suppress the attacks in the early morning. The half-lives of ramelteon and its metabolites are suitable for treating insomnia, but may be too short for all day relief from cluster headaches.

The present case indicated that ramelteon immediately suppressed the cluster headache attacks during sleep and showed no adverse effects. Ramelteon may be an adjunctive preventive therapy for cluster headaches with attacks during sleep.

The author states that he has no Conflict of Interest (COI).

References


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