

## Ramelteon in the Prophylaxis of Chronic Cluster Headache-Case Report

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Received: December 9, 2014 Revised: February 6, 2014

Accepted: February 9, 2015

Published online: May 13, 2015

### ABSTRACT

Cluster headache is a primary headache characterized by severe pain with most attacks occurring during sleep. This is a case report on the use of ramelteon as a treatment for chronic cluster headache. A 42-year-old businessman, who had been experiencing episodic cluster headaches for 10 years, was diagnosed with chronic cluster headache in the past year during which time his activities of daily living had been greatly reduced because of daily cluster headache attacks. We initiated treatment with ramelteon (8 mg/day) prophylactically before sleep, and his average attack frequency per day after taking the drug was less than that before taking the drug. The elimination half-life of ramelteon is typically under 2 h, whereas that of melatonin is typically 30 min. This difference in the elimination half-life may have caused the better response to ramelteon treatment than to melatonin. We conclude that ramelteon may be useful as a new agent in both the prevention and prophylaxis of chronic cluster headache, when attacks occur at the same time during the night and that cluster headache is related to circadian rhythm.

**Key words:** Cluster headache; Ramelteon; Melatonin; Circadian Rhythm; Prophylaxis

Hamada Y, Saigoh K, Mitsui Y, Kikui S, Takeshima T, Kusunoki S. Ramelteon in the Prophylaxis of Chronic Cluster Headache-Case Report. *International Journal of Neurology Research* 2015; 1(1): 93-95 Available from: URL: <http://www.ghrnet.org/index.php/ijnr/article/view/964>

### INTRODUCTION

The clinical features of cluster headache (CH) are a headache that is usually lateralized, often with prominent, cranial, parasympathetic autonomic features, which are also lateralized and ipsilateral to the headache (ICHD-IIIβ: 3.1)<sup>[1]</sup>. Approximately 10%-15% of patients with chronic cluster headache (CCH) do not have remission periods<sup>[2]</sup> (ICHD-IIIβ: 3.1.2)<sup>[1]</sup>. Unlike episodic cluster headache (ECH) attacks, which occur in periods lasting from seven days to one year, separated by pain-free periods lasting at least one month (ICHD-IIIβ: 3.1.1)<sup>[1]</sup>, CCH attacks occur for more than one year without remission or with remission periods lasting less than one month.

CCH is an intractable headache and reduces the ability of the patient to perform activities of daily living (ADLs). CCH occurs daily without remission periods. CH may be caused by a decrease in nocturnal melatonin levels and a loss of melatonin rhythm<sup>[3]</sup>. In a small double-blind, placebo-controlled study in 20 patients with CH, melatonin reduced CH frequency compared with the placebo<sup>[4]</sup>. Ramelteon is the first in a new class of sleep agents and is a melatonin receptor agonist for both MT1 and MT2 receptors<sup>[5]</sup>. There are currently no studies describing the effectiveness of ramelteon in the prophylaxis of CCH. To the best of our knowledge, this is the first report on the use of ramelteon as a preventive treatment for CCH.

### METHOD

We obtained informed consent from the patient for treatment with ramelteon after explaining its side effects. The study was approved

by our hospital's review board and was therefore performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and all subsequent revisions.

Headache pain of parameters used to average attack frequency per day.

## CASE REPORT

A 42-year-old businessman had been experiencing one-sided, episodic, and excruciating headaches for 10 years. Seven years ago, he visited our hospital for a check-up. He had no other diseases, and there were no abnormal findings on brain magnetic resonance imaging. The headaches occurred three to five times per day with lacrimation, rhinorrhea, and miosis on the affected side, accompanied by a sense of restlessness and agitation. The headaches and secondary symptoms continued for approximately 90 min every day during a one-month period every summer. He was diagnosed with ECH as he fulfilled the necessary diagnostic criteria<sup>[1]</sup>. We started therapy with 7 L/min oxygen and 50 mg sumatriptan. The response to oxygen therapy was mild and lasted for approximately 30 min, and treatment with sumatriptan by oral administration was not effective in preventing the cluster attacks.

Four years ago, we started sumatriptan treatment via 3 mg subcutaneous injection for the CH attacks. The response to the subcutaneous sumatriptan injection treatment was good and had a fast effect within approximately 10 min. Therefore, we taught the patient to self-administer sumatriptan subcutaneously. Three years ago, the ECH attacks began to occur daily from March to April, as well as during the one summer month. Nevertheless, the patient continued to self-administer 3 mg sumatriptan subcutaneously for the attacks.

A few months before our follow-up period (Figure 1), the CH attacks reduced in their frequency with remission periods, and the response to subcutaneous sumatriptan injection treatment remained very good.

However, the period between CH attacks was eight months, which was different from before because within one month, the attacks occurred again.

By 12 months (Figure 1), the CH attacks were occurring throughout the 11 months without 1-month periods of pain-free remission. He was therefore diagnosed with CCH because he fulfilled the criteria<sup>[1]</sup>. We then tried an alternative treatment using verapamil 240 mg/day, lomerizine 10 mg/day, and sodium valproate 600 mg/day. However, these agents were not effective against the CCH attacks, and only subcutaneous sumatriptan treatment produced a satisfactory response against the attacks. Following the use of prednisolone (0.5 mg/kg) before sleeping, the attacks did not occur during the day but began to occur 2 h after going to bed every night. We hypothesized that his attacks were connected with circadian rhythm and basic sleep disturbance and attempted using prophylactic ramelteon (8 mg/day), administered every night before the patient went to sleep. The patient's average attack frequency per day was less after taking the drug than that before taking the drug (Figure 1). His sleep disturbance also returned to a normal rhythm. He did not experience any direct or collateral side effects such as dizziness or daytime sleepiness with ramelteon treatment. CH attacks are now very infrequent and occur only several times a month. The patient continues to use ramelteon alone as an effective treatment.

## DISCUSSION

CHs are classified into two subtypes: ECH and CCH. CCHs are rarer with only 10%-15% of cluster headaches being classed as chronic<sup>[2]</sup>.

CCHs are continuous, excruciating headaches without pain-free intervals. CCHs are also intractable and adversely affect the ability to perform ADLs. Melatonin may be involved in CH attacks. Chazot *et al.*<sup>[3]</sup> have reported a decrease in melatonin secretion at night and disappearance of melatonin rhythm in patients with CH. Plasma melatonin levels decreased and there was no melatonin rhythm either in non-rapid eye movement sleep, rapid eye movement sleep, or waking during cluster periods. However, plasma melatonin levels did not decrease and had normal rhythm during remission periods<sup>[6]</sup>. Melatonin treatment for CH has only been studied in a small, double-blind, placebo-controlled trial. This trial reported a significant decrease in CH attacks in the melatonin-treatment group when compared with the placebo group<sup>[4]</sup>. However, a more recent double-blind, placebo-controlled trial using melatonin treatment for CH did not report a significant difference in attacks<sup>[7]</sup>. Therefore, response to melatonin treatment for CCH differs between reports<sup>[8,9]</sup>.

Ramelteon is the first in a new class of sleep agents and is a melatonin receptor agonist with both high affinity and selectivity for melatonin MT1 and MT2 receptors than for MT3 receptors. The activity of ramelteon at the MT1 and MT2 receptors is believed to improve sleep and the maintenance of circadian rhythm that determines the normal sleep-wake cycle<sup>[5]</sup>. The elimination half-life of ramelteon is typically under 2 h, whereas that of melatonin is typically 30 min. The difference in the elimination half-life may cause a better response to ramelteon treatment than to melatonin treatment.

Only one previous case report in Japan has documented the effectiveness of ramelteon in a patient with ECH<sup>[10]</sup>. This report used ramelteon for a very short period. In our case, ramelteon was used in the patient with CCH for a longer period. We suspect that ramelteon adjusted and stabilized the patient's melatonin level and circadian rhythm<sup>[11,12]</sup>. No other study has shown the effectiveness of ramelteon in the treatment of CCH. Ramelteon may be useful as a new agent in the preventive treatment of CCH when attacks occur at the same time during the night and when CH is related to circadian rhythm. Furthermore, ramelteon may be used at night prophylactically in CH.

## ACKNOWLEDGMENTS

This study was supported in part by the Ministry of Health, Labor, and Welfare of Japan [Research on intractable diseases (H26-69)] and the Ministry of Education, Culture, Sports, Science, and Technology of Japan (Grants-in-Aid for Scientific Research, 24390225)

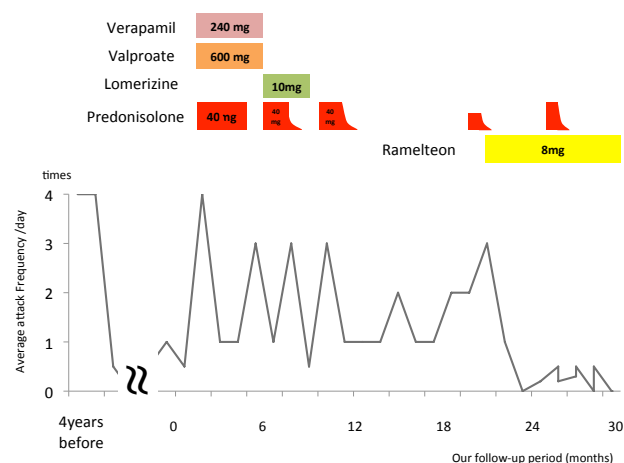


Figure 1 Clinical course of CCH.

## CONFLICT OF INTERESTS

The Authors have no conflicts of interest to declare.

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