

[ORIGINAL ARTICLE]

Naratriptan in the Prophylactic Treatment of Cluster Headache

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Abstract:

Objective Naratriptan has been reported to reduce the frequency of cluster headache. The purpose of this study was to determine whether naratriptan is effective as a prophylactic treatment for cluster headache in Japan.

Methods We retrospectively reviewed all 43 patients with cluster headache who received preventive treatment with naratriptan from April 2009 to April 2015. The International Classification of Headache Disorders, 3rd Edition (beta version) (ICHD-3 beta) was used to diagnose cluster headache. This study was conducted at 3 centers (Department of Neurology, Saitama Medical University; Saitama Neuropsychiatric Institute; Saitama Medical University International Medical Center). Patients were recruited from these specialized headache outpatient centers. Naratriptan was taken before the patient went to bed.

Results The study population included 30 men (69.8%) and 13 women (30.2%). Twenty-two cases received other preventive treatments (51.2%), while 21 cases only received naratriptan (48.8%). Among the 43 cases, 37 patients (86.0%) achieved an improvement of cluster headache on naratriptan.

Conclusion Naratriptan has been suggested as a preventive medicine for cluster headache because of the longer the biological half-life in comparison to other triptans. The internal use of naratriptan 2 hours before attacks appears to achieve a good response in patients with cluster headache.

Key words: cluster headache, naratriptan, prophylactic treatment

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Introduction

The subcutaneous injection of sumatriptan is reportedly effective in the acute treatment of cluster headache (1, 2). Its effectiveness in this regard has been demonstrated in Japan (3). Pure oxygen delivered via the side tube of a face mask at 7 L/min for 15 minutes has also been reported as useful (3). On the other hand, among the calcium channel blockers, verapamil (360 mg/day) has been shown to have prophylactic effects overseas. However, the adverse effect of delayed cardiac conduction causing bradycardia and heart failure is a matter of concern (4). Ergotamine tartrate (1-2 mg) taken orally before bedtime may be effective as prophylaxis (3). Civamide (a structural analog of capsaicin) nasal

spray has also been reported to be effective overseas (5), but no clinical trials have been conducted in Japan. Corticosteroids are also considered effective, but clear evidence is lacking (6). Furthermore, these medications are not always effective for all patients and may have side effects. In this way, few therapies are effective for preventing cluster headache. Naratriptan, a 5-hydroxytryptamine_{1B/D} (5-HT_{1B/D})-agonist, appears effective as a pharmacotherapy for migraine. Naratriptan has also been reported to reduce the frequency of cluster headache (7-9).

We chose naratriptan as a prophylactic therapy for cluster headache due to its pharmacokinetic properties, which include a long half-life and improved bioavailability in comparison to other 5-HT agonists (10). The purpose of this study was to determine whether naratriptan would be effective

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tive in the prophylactic treatment of cluster headache in Japan.

Materials and Methods

We retrospectively reviewed all 43 patients with cluster headache who orally agreed to receive preventive treatment with naratriptan from April 2009 to April 2015. This study was approved as a retrospective study by the institutional review boards at Saitama Medical University, Saitama Neuropsychiatric Institute, and Saitama Medical University International Medical Center (approval number; 15-132-2).

In our clinical case studies, we wanted to establish a basis for a randomized control study near future.

We initially used the International Classification of Headache Disorders, 2nd edition (ICHD-2) (11); since 2013, we have used the International Classification of Headache Disorders, 3rd Edition (beta version) (12) as diagnostic criteria for cluster headache. The patients were recruited from 3 specialized headache outpatient centers: the Department of Neurology at Saitama Medical University; Saitama Neuropsychiatric Institute; and Saitama Medical University International Medical Center.

Naratriptan was taken before the patient went to bed. We assessed whether improvements were achieved in cluster headache attacks by the prophylactic administration of naratriptan. We analyzed the age, sex, dose of naratriptan, and the use of other preventive agents. We defined "effective" as the complete disappearance of headache attacks and "non-effective" as the incomplete disappearance of headache attacks.

Results

Table shows a clinical summary of the patients with cluster headache who were treated with naratriptan. The 43 patients included 30 men (69.8%) and 13 women (30.2%). The mean age of the patients was 42.7 years. Twenty-two patients were receiving other preventive treatments (51.2%), whereas 21 only received naratriptan (48.8%). Among all 43 cases, 37 patients (86.0%) showed an effective improvement of cluster headache with naratriptan, while naratriptan had little or no effect in 6 cases (14.0%).

These patients were secondarily classified into 4 categories according to their clinical features (Table).

a. The use of naratriptan alone

Nineteen patients (44.2%) showed an effective improvement of cluster headache with the use of naratriptan alone. In Case 1 (as a typical case), naratriptan alone was effective in preventing headache attacks. The patient was a 40-year-old man with episodic cluster headache. Headache attack periods always lasted for approximately 2-3 months of the year, and he had always experienced headache attacks within this period at a rate of approximately once every 24 hours. After the initial administration of naratriptan, the

headache attack period was reduced to less than 1 month.

b. The lack of effectiveness of naratriptan

Naratriptan was ineffective in preventing cluster headache in 6 patients (14.0%). The two following cases show characteristic clinical courses.

Case 20 involved a 39-year-old man with episodic cluster headache. Sumatriptan had been effective for his headaches, but the possibility of medication-overuse headache (MOH) needed to be addressed. The administration of naratriptan once daily had reduced the frequency of headaches, and - along with lomerizine and amitriptyline - achieved freedom from headaches. However, the headache symptoms might have shown spontaneous remission.

Case 21 involved a 34-year-old woman with episodic cluster headache. Ergotamine before bedtime had previously been effective in preventing headache attacks. Remission lasted for approximately one month, but she still experienced headaches around once every 24 hours. The administration of naratriptan 1 hour before the onset of headache symptoms had no discernible effect. However, the administration of naratriptan 2 hours before the onset of headache symptoms reduced the frequency of headache attacks.

c. The usage of naratriptan with other preventive drugs

The cluster headache of 16 patients (37.2%) showed effective improvement with the use of naratriptan and other preventive drugs. In Case 26 (as a typical case), the use of naratriptan with other preventive drugs was effective. The patient was a 52-year-old man who had experienced episodic cluster headache since he was 20 years of age. Remissions lasted approximately 1-5 months. Although he was taking verapamil (240 mg/day), prednisolone (40 mg/day), and nasal drops of sumatriptan, he still experienced headaches. The addition of naratriptan once daily reduced the frequency; however, the headaches remained. The addition of lomerizine and amitriptyline achieved freedom from headaches.

d. Naratriptan twice daily with other preventive drugs

Two patients (4.7%) showed effective improvement of cluster headache with the use of naratriptan twice daily with other preventive drugs. Case 42 (as a typical case) involved a 24-year-old woman with episodic cluster headache. She experienced headache once every 24-36 hours. Prophylactic therapy with sodium valproate had proven unsuccessful. The administration of naratriptan twice daily reduced the frequency and severity of headache. Because this patient showed an irregular timing of attacks, naratriptan was administered twice a day.

Discussion

Most of our patients found relief following the introduc-

Table. A Clinical Summary of the Patients with Cluster Headache who were Treated with Naratriptan.

a. The use of naratriptan alone (n=19)

Case No.	Age Sex	Dose of naratriptan	Improvement	Other preventive treatments
1.	40 M	2.5 mg	effective	none
2.	27 M	2.5 mg	effective	none
3.	50 M	2.5 mg	effective	none
4.	45 M	5 mg	effective	none
5.	55 M	2.5 mg	effective	none
6.	31 F	2.5 mg	effective	none
7.	46 M	2.5 mg	effective	none
8.	57 M	2.5 mg	effective	none
9.	52 M	2.5 mg	effective	none
10.	44 M	2.5 mg	effective	none
11.	23 M	2.5 mg	effective	none
12.	22 F	2.5 mg	effective	none
13.	34 F	2.5 mg	effective	none
14.	35 M	2.5 mg	effective	none
15.	71 F	2.5 mg	effective	none
16.	58 F	2.5 mg	effective	none
17.	39 F	2.5 mg	effective	none
18.	31 M	2.5 mg	effective	none
19.	37 M	2.5 mg	effective	none

b. The lack of effectiveness of naratriptan (n=6)

Case No.	Age Sex	Dose of naratriptan	Improvement	Other preventive treatments
20.	39 M	2.5 mg	non-effective	none
21.	34 F	2.5 mg	non-effective	none
22.	37 F	2.5 mg	non-effective	verapamil
23.	26 F	2.5 mg	non-effective	verapamil
24.	55 M	2.5 mg	non-effective	verapamil, prednisolone
25.	71 M	2.5 mg	non-effective	verapamil, prednisolone

c. The usage of naratriptan with other preventive drugs (n=16)

Case No.	Age Sex	Dose of naratriptan	Improvement	Other preventive treatments
26.	52 M	2.5 mg	effective	verapamil
27.	29 M	2.5 mg	effective	verapamil, prednisolone
28.	63 F	1.25 mg	effective	lomerizine
29.	24 M	2.5 mg	effective	lomerizine
30.	36 M	2.5 mg	effective	verapamil
31.	45 F	2.5 mg	effective	verapamil
32.	47 M	2.5 mg	effective	verapamil, prednisolone
33.	49 M	2.5 mg	effective	verapamil
34.	38 M	2.5 mg	effective	verapamil
35.	49 M	2.5 mg	effective	verapamil
36.	49 M	2.5 mg	effective	verapamil, sodium valproate
37.	36 F	2.5 mg	effective	verapamil
38.	61 M	2.5 mg	effective	sodium valproate
39.	52 M	2.5 mg	effective	propranolol
40.	47 M	2.5 mg	effective	chotosan
41.	38 M	2.5 mg	effective	verapamil, prednisolone, chotosan

d. Naratriptan twice daily with other preventive drugs (n=2)

Case No.	Age Sex	Dose of naratriptan	Improvement	Other preventive treatments
42.	24 F	5 mg	effective	sodium valproate
43.	41 M	5 mg	effective	verapamil

tion of daily naratriptan. We believe that these improvements were not due to the coincidental remission of cluster headache. Naratriptan offers a long half-life and improved bioavailability in comparison to other 5-HT agonists (7).

This difference in pharmacokinetics may explain why Monstad did not find prophylactic treatment with sumatriptan to be effective for patients with cluster headache (13). The first dose should usually be administered before bed. In some patients, a second dose is needed in the morning to prevent daytime or irregular attacks.

The administration of naratriptan 2 hours before attacks appears to achieve a good response in patients with cluster headache. Incidentally, 81.4% of the patients in the naratriptan alone group and the naratriptan and other preventive drugs group to naratriptan 2 hours before their attacks.

We consider naratriptan to be a promising new prophylactic agent for refractory cluster headache. Provided that safety issues with daily usage are resolved, naratriptan may replace other prophylactic drugs in cases with too many side effects.

We encountered a small proportion of patients who might have experienced spontaneous remission, and other cases in which naratriptan was ineffective against headache attacks. Some cases used other preventive drugs along with naratriptan. This study reached the limits of interpretation for a retrospective case study and review. Thus, a double-blind placebo-controlled study using naratriptan as a preventive treatment for cluster headache is needed to provide further insight regarding this treatment modality in the near future.

Clinical implications

- The administration of naratriptan 2 hours before attacks appears to achieve a good response in patients with cluster headache.

- Provided that safety issues with daily usage are resolved, naratriptan may replace other prophylactic drugs in cases with too many side effects.

- A double-blind placebo-controlled study using naratriptan as a preventive treatment for cluster headache is needed to provide further insight regarding this treatment modality

in the near future.

The authors state that they have no Conflict of Interest (COI).

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