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## Clinical efficacy of rizatriptan for patients with migraine: efficacy of drug therapy for migraine accompanied by tension headache-like symptoms, focusing on neck stiffness

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**Abstract** According to an epidemiological study in Japan, there are as many as 22 million patients with tension headache and 8.4 million with migraine. Furthermore, patients suffering from both types of headache concurrently are estimated to account for more than 50% of headache patients. We studied the efficacy of drug therapy for migraine accompanied by tension headache-like symptoms, focusing principally on neck stiffness. We evaluated the efficacy of rizatriptan by comparison of findings before and after therapy in 34 migraine patients, consisting of 16 without neck stiffness (migraine without neck factor: WONF) and 18 with it (migraine with neck factor: WNF), who received treatment at our neurology/internal medicine department from 1 March 2004 to 31 May 2005. In the study, all the patients were asked to keep a record of their migraine status. The severity of migraine was classified by physicians according to the International Headache Society diagnostic criteria, based on which drug efficacy was evaluated. We selected rizatriptan for migraine treatment in our study based on

Dr. Ferrari's report. In the efficacy study of rizatriptan, in the group of 34 migraine patients, the pain relief rate (79.4%) and pain-free rate (41.2%) at two hours after treatment were as high as those reported in the meta-analysis performed by Ferrari et al., indicating high efficacy of rizatriptan. In the efficacy comparison between the WONF and WNF groups, the pain-free rates were 56.3% and 27.8%, and cumulative pain relief rates were 100% and 61.1%, respectively, with better results in the WONF group. A test result was also significantly better ( $p=0.0076$ ) in the WONF group. Rizatriptan was proved effective in treating migraine patients accompanied by tension headache-like symptoms. Comparison of efficacy rates between patient groups with and without tension headache-like symptoms showed that the pain relief rate in the group without neck stiffness was higher.

**Keywords** Neck stiffness • Tension headache • Migraine • 5-HT<sub>1B/1D</sub> receptor agonist • Rizatriptan

## Introduction

While their causes are diverse, headaches that are recurrent and have no organic disease as their cause are classified as primary headaches (chronic headache), and are represented by migraine, tension headache and cluster headache. Among these three, tension headaches are the most frequently reported epidemiologically.

There are reports, however, that many patients visiting medical facilities for treatment of self-reported symptoms characteristic of tension headache and other chronic headaches were actually suffering from migraine, resulting in inappropriate diagnosis and treatment [1–4].

While neck stiffness is widely regarded as a symptom accompanying tension headache, it is also frequently observed in migraine patients, a finding not well understood by either physicians or patients themselves. This often leads to diagnosis and treatment of migraine as tension headache. Another reason for frequent incorrect diagnosis of migraine as tension headache is related to shifts in the site at which pain occurs during a migraine attack: for example, pain on one side of the head sometimes spreads to both sides, and non-pulsatile pain at the beginning of an attack often shifts to pulsatile pain at the most advanced stage of the headache. For these reasons, if a patient complains of bilateral and non-pulsatile pain, the condition may be diagnosed as tension headache even though there are other factors indicating migraine.

According to an epidemiological study in Japan, there are 22 million patients with tension headache and 8.4 million with migraine, both of which are thus high in incidence. Furthermore, patients suffering from both concurrently are estimated to account for more than 50% of headache patients. We therefore studied the efficacy of drug therapy for migraine, focusing on the symptom of neck stiffness.

## Methods

We evaluated the efficacy of rizatriptan by comparison of findings before and after therapy in 34 migraine patients, consisting of 16 without neck stiffness (migraine without neck factor: WONF) and a mean age of  $33.5 \pm 8.8$  years and 18 with it (migraine with neck factor: WNF) and a mean age of  $37.1 \pm 11.2$  years, who received treatment at our neurology/internal medicine department from 1 March 2004 to 31 May 2005.

All the patients were asked to keep a record of their migraine status at designated times. The severity of migraine was classified by physicians according to the International Headache Society diagnostic criteria, based on which efficacy was evaluated by comparison of findings before and after therapy.

## Study design

We selected rizatriptan for migraine treatment in our study based on a report by Ferrari et al. published in *The Lancet* in 2001 [5].

Patients were asked to fill in the chronic headache check sheet, which had been provided in advance, so as to obtain a better understanding of their types of headaches. In addition, they were asked to keep a record of their migraine status to gather data on the severity and frequency of headaches, based on which physicians evaluated severity and efficacy of treatment. The severity of headaches and impact on daily life were recorded using a three-level scale (3 for severe, 2 for moderate and 1 for mild) before receiving rizatriptan and a four-level scale (3 for severe, 2 for moderate, 1 for mild and 0 for none) two hours after receiving rizatriptan and whenever an attack occurred in the morning, afternoon or at night.

## Statistical analysis

Distributions of baseline characteristics of patients before therapy in the two groups were analysed by Fisher's exact probability test, and statistical data such as age and disease period by the unpaired *t*-test. Differences in efficacy judgements between the two groups were analysed using the Mann-Whitney *U*-test. The significance level for all tests was 5%.

## Results

Table 1 shows the characteristics of the subject groups and headache severity before therapy. There were more females among the evaluable subjects. The mean disease periods in the WONF and WNF groups were 34.4 and 33.5 months, and the mean numbers of attacks 6.4 and 6.5, respectively, with no significant differences between the two groups. The mean attack durations in the WONF and WNF groups were  $3.8 \pm 2.39$  (mean  $\pm$  SD) and  $6.5 \pm 4.07$  (mean  $\pm$  SD) ( $p=0.0858$ ). There were no differences in distributions of age, severity of headache or presence/absence of pressure pain between the two groups. The administration times varied from patient to patient: some took the medication at a signalling stage and others immediately after a headache attack or at the most advanced stage. The mean time of administration after start of a headache was  $5.5 \pm 2.0$  h.

Table 2 shows the result of efficacy comparison for rizatriptan. For the group of all 34 migraine patients, the pain relief and pain-free rates at two hours after treatment were 79.4% and 41.2%, respectively, demonstrating efficacy as high as that reported in the meta-analysis conducted by Ferrari et al. [5]. In a comparison between the

**Table 1** Baseline characteristics

Item	Category	Migraine without neck factor group	Migraine with neck factor group	<i>p</i> -value
Age, years		33.5±8.75 ( <i>n</i> =16)	37.1±11.16 ( <i>n</i> =18)	0.3060
Sex	Male:female	4:12	4:14	0.5826
Disease period, months		34.4±43.44 ( <i>n</i> =8)	33.5±28.35 ( <i>n</i> =10)	0.9595
Severity of headache	Moderate:severe	13:3	14:4	0.5708
Frequency of headache, hours		6.4±3.01 ( <i>n</i> =16)	6.5±2.98 ( <i>n</i> =18)	0.9519
Mean attack duration, hours		3.8±2.39 ( <i>n</i> =12)	6.5±4.07 ( <i>n</i> =10)	0.0858
Presence/absence of pressure pain	Presence:absence	5:11	6:11	0.5493

**Table 2** Result of efficacy comparison

	Disappeared, <i>n</i> (%)	Improved, <i>n</i> (%)	No change	Mann-Whitney
Migraine without neck factor group	9 (56.3)	7 (100)	0	<i>p</i> =0.0076
Migraine with neck factor group	5 (27.8)	6 (61.1)	7	
Total	14 (41.2)	13 (79.4)	7	

WONF and WNF groups, the pain-free rates were 56.3% and 27.8% and cumulative pain relief rates were 100% and 61.1%, respectively, with better results in the WONF group. The Mann-Whitney test result confirmed the significant superiority (*p*=0.0076) of the WONF group.

## Discussion

Migraine interferes with daily life, not only decreasing patients' quality of life but that of their families. According to a report, of patients with chronic headache who complained of adverse impacts on their daily lives, 90% were suffering from migraine and 10% from tension headache [6], indicating a significant difference in impact on daily life and activities between the two types of headache. Medication, if it is properly administered, would be one option to mitigate the impact of migraine on daily life and activities.

Rizatriptan [7–9], the investigational drug in our study, is a second-generation 5-HT<sub>1B/1D</sub> receptor agonist, in association with which very few adverse drug reactions have been reported. Sheftell et al. [10] reported that patients receiving rizatriptan experience switching to other drugs least frequently. Ninan et al. [11] reported that the pain-free rate in migraine patients receiving rizatriptan at an early stage was significantly higher than those for patients receiving other triptans.

Both physicians and patients are poorly aware of the fact that neck stiffness is frequently observed among migraine patients. Physicians often diagnose patients as suffering from tension headache simply because patients

complain of headache associated with a stiff neck. We therefore evaluated the efficacy of rizatriptan, mainly focusing on neck stiffness, in 16 patients without neck stiffness (WONF) and 18 with it (WNF).

Blau et al. [12] reported that neck stiffness could induce migraine. Kaniecki and Totten [13] reported that 75% of migraine patients concurrently suffer from neck pain, which occurs at any of the stages: signalling, headache or mitigating. They also reported that it is difficult in the clinical setting to correctly diagnose whether the condition is migraine or tension headache, and that therefore physicians should select a medication that can treat the symptoms of both [14]. In their report, they added that sumatriptan therapy in migraine patients accompanied by neck stiffness and other tension-type symptoms successfully improved both headache and tension-type symptoms. In our study, rizatriptan therapy exhibited efficacy in pain relief in the WNF regardless of when neck stiffness occurred, along with or before or after an attack. Despite confirmation of efficacy, the pain relief and pain-free rates in the WNF group were lower than those in the WONF group. Furthermore, the level of satisfaction with efficacy of therapy was lower in the WNF group, even for those where headache disappeared or was improved, than for those in the WONF group, and re-onset of neck stiffness with regard to rizatriptan was 36.4%.

The neck stiffness in the WNF group was different in nature from that associated with tension headache. In patients with chronic stiff neck, the symptom tends to become stronger when a headache occurs. Neck stiffness that occurred at the onset of headache was very likely to be classified as radiating pain in the cervical area through the

spinal trigeminal nucleus. If more than one type of neck stiffness is observed in migraine patients, responses to rizatriptan therapy could also vary. This can explain the significant differences in pain relief and pain-free rates between the WONF and WNF groups. All things considered, in treating migraine patients with neck stiffness, use of eperisone hydrochloride or other drugs in addition to rizatriptan might be effective. For migraine patients with chronic neck stiffness, preventive measures should also be considered.

Rizatriptan therapy was found in this study to be effective in both migraine patient groups with and without neck stiffness. When patients with chronic headache chiefly complain of headaches severe enough to interfere with their daily lives, physicians should suspect migraine,

regardless of the occurrence of neck stiffness, in diagnosis and provision of appropriate treatment.

## Conclusions

Our study demonstrated the efficacy of rizatriptan in improving headache symptoms in migraine patients with neck stiffness. We recommend use of drug therapy in accurately diagnosed migraine patients with neck stiffness. We have suggested that although neck stiffness does not make triptans ineffective, coadministration might improve outcome.

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