

# Intranasal Sumatriptan Study with High Placebo Response in Taiwanese Patients with Migraine

Shuu-Jiun Wang\*, Jong-Ling Fuh, Zin-An Wu

*Neurological Institute, Taipei Veterans General Hospital and National Yang-Ming University School of Medicine, Taipei, Taiwan, R.O.C.*

**Background:** Triptan's efficacy in the treatment of migraine has never been reported in Taiwanese. A high placebo effect was reported in Japanese. The objective of this study was to evaluate the efficacy of intranasal sumatriptan in the acute treatment of migraine in Taiwanese patients.

**Methods:** Fifty-eight patients who had experienced migraine for at least 1 year were randomly assigned to 2 groups, self-administered intranasal sumatriptan 20 mg or placebo to treat a single migraine attack of moderate or severe intensity.

**Results:** A significant difference in headache relief rates between the 2 groups was observed at 30 minutes postdose (46% vs. 21%,  $p < 0.05$ ). One hour postdose, 61% of sumatriptan recipients experienced headache relief compared with 43% of placebo recipients ( $p = 0.181$ ). The difference in relief rates between groups diminished over time, mainly due to a high placebo response (54% at 2 hours postdose).

**Conclusion:** Our study suggests that ethnicity might have a role in placebo response, and highlights the importance of a placebo group in acute migraine trials. However, the small sample size in this study should also be taken into consideration. [*J Chin Med Assoc* 2007;70(2):39–46]

**Key Words:** Asian, intranasal, migraine, placebo, sumatriptan

## Introduction

Migraine headache was believed to be much less prevalent among Asians than in Western populations.<sup>1</sup> However, many surveys involving Asians were limited by flaws in methodology and case definition criteria. Using a validated questionnaire, a population-based survey conducted in Taiwan showed that the 1-year prevalence of migraine was 9.1% (4.5% in men, 14.4% in women).<sup>2</sup> This figure is similar to those involving Western populations.<sup>1</sup>

Sumatriptan is commonly prescribed to treat acute migraine attacks.<sup>3</sup> It was initially available as a subcutaneous injection, and then as an orally administered tablet, and later as an intranasal spray. The intranasal formulation allows patients to avoid injections while providing more rapid absorption and slightly reducing hepatic first-pass compared with oral administration. Several clinical trials have evaluated the efficacy of

intranasal sumatriptan in providing relief from migraine attacks. Two dose-ranging studies showed that sumatriptan 10 mg and 20 mg were significantly more effective than placebo, with the 20-mg dose emerging as optimal.<sup>4</sup>

At present, there is a paucity of data regarding the efficacy of intranasal sumatriptan in the acute treatment of migraine in Asian patients. In a comprehensive review involving 2,307 patients, only 7 were Asian.<sup>5</sup> This review showed that clinical trials involving triptans consistently demonstrate efficacy across ethnic groups; however, the relative magnitude of the benefit may vary. Placebo response in triptan trials may have influenced the demonstrated relative benefit of triptans in Asians. A clinical trial evaluating the efficacy of eletriptan in Japanese migraineurs showed that the placebo group had a high headache relief rate (51%) at 2 hours postdose.<sup>6</sup> Consistency of this observation in other Asian subpopulations may be explored.

\*Correspondence to: Dr Shuu-Jiun Wang, Neurological Institute, Taipei Veterans General Hospital, 201, Section 2, Shih-Pai Road, Taipei 112, Taiwan, R.O.C.

E-mail: sjwang@vghtpe.gov.tw • Received: July 17, 2006 • Accepted: December 22, 2006

The primary objective of this study was to compare the efficacy, including speed of effect onset, and the safety and tolerability of intranasal sumatriptan 20 mg with that of placebo in the acute treatment of migraine among Taiwanese patients.

## Methods

### *Patients*

Patients from a neurologic outpatient clinic of a medical center in Taipei, 18–65 years old, with a history of migraine, with or without aura (as defined by the International Headache Society criteria<sup>7</sup>), for the past 12 months were recruited into the study. Patients were required to have experienced 1–6 episodes of moderate to severe migraine attacks per month during the last 3 months prior to study enrollment, and were required to distinguish migraine from non-migraine headaches.

Demographic data, current medical status, migraine history and concurrent medications of eligible patients were recorded. Patients were excluded from the study if they had tension-type headaches for >15 days in a month during the previous 12 months, had been exposed to intranasal sumatriptan at least 3 months prior to the study; or had a known hypersensitivity to sumatriptan. Patients receiving ergotamine- or dihydroergotamine-containing prophylactic migraine medication, monoamine oxidase inhibitors, or lithium were also excluded. Other exclusion criteria included the following: pregnancy; breastfeeding; abuse of opiates or psychotropic drugs, whether current or during the previous 2 years; abuse of ergotamine (defined as >10 mg weekly), whether current or during the previous 12 months; current abuse of alcohol or other drugs; ischemic heart disease; coronary vasospasm; atherosclerotic disease; and treated or untreated hypertension. Patients who normally received prophylactic migraine medications were allowed to continue prophylaxis, provided that their prophylaxis regimen did not contain ergotamine or dihydroergotamine.

### *Procedures*

This was a single-center, randomized, double-blind, placebo-controlled, parallel-group study. The study protocol was approved by the hospital's institutional review board and the Taiwan Department of Health. All patients provided their written informed consent before study enrollment.

After screening, patients were randomized using a computer-generated, parallel design by 1:1 ratio (block size of 4) into 2 groups given either intranasal

sumatriptan 20-mg spray or a placebo spray with identical appearance. Patients were instructed to administer a single intranasal dose at the onset of a moderate or severe migraine attack, with or without aura. They were also instructed to withhold the study medication within 6 hours of taking an analgesic or an antiemetic. If the headache resolved or improved to mild severity within 2 hours after the first dose, but worsened to moderate or severe intensity from 2 to 24 hours post-dose, a second identical dose was allowed to treat the recurrence. If patients experienced insufficient pain relief, they were allowed to use their usual non-sumatriptan rescue medications 120 minutes after administration of the study medication.

### *Outcome assessments*

Response to treatment and usage of rescue medication, if any, were recorded on a diary card. Patients assessed headache intensity and then recorded the pain rating on a diary card using a 4-point pain scale (0 = no pain, 1 = mild pain, 2 = moderate pain, 3 = severe pain). This was done immediately before administering the first intranasal dose, and after 15, 30, 45, 60, 90 and 120 minutes. The following were also recorded on the diary card: associated symptoms (e.g. nausea, vomiting, phonophobia and photophobia); time to normal function (a subjective feeling of "meaningful relief" of migraine headache and/or associated symptoms); time to complete relief of migraine (absence of pain and associated symptoms); taste (very unpleasant, unpleasant, no taste, pleasant or very pleasant); patient's overall rating of the study medication (very poor, poor, reasonable, good or excellent); and adverse events.

Headache relief was defined as reduction in headache pain intensity from moderate/severe (pain rating of 2/3) to mild/no pain (1/0). The primary efficacy endpoint was headache relief at 60 minutes. Secondary efficacy endpoints included headache relief rates at 15, 30, 45, 90 and 120 minutes; percentages at each time interval of headache-free patients (i.e. headache resolution, no headache at all) and those with no nausea, vomiting, photophobia or phonophobia; and percentage of patients requiring rescue medication between 2 and 24 hours after receiving the study medication.

Patients were instructed to return to the clinic 24 hours after the final administration of the test drug to return their diary card. Adverse events and biochemical profiles were also assessed during this visit.

### *Statistical analysis*

Analysis was conducted on an intent-to-treat basis. All statistical tests were 2-sided, with a significance level of 0.05. Based on literature review, headache relief at

2 hours was around 70% in the triptan group and 30% in the placebo group.<sup>8</sup> Therefore, it was estimated that at least 23 evaluable patients in each group were needed to detect the statistical difference between them at the 5% level of significance with 80% power. The  $\chi^2$  test was used to compare the primary efficacy endpoint of rate of headache relief at 60 minutes postdose. Secondary endpoints were compared using the  $\chi^2$  or Fisher's exact tests. The median times to functional recovery and complete recovery were compared by nonparametric Mann-Whitney test, and the interquartile range (the distance between the 75<sup>th</sup> percentile and the 25<sup>th</sup> percentile) was also provided. The percentage of patients taking a second dose of study medication to treat recurrence, percentage of patients experiencing relief after the second dose of study medication, and taste rating were described but not subjected to statistical analysis.

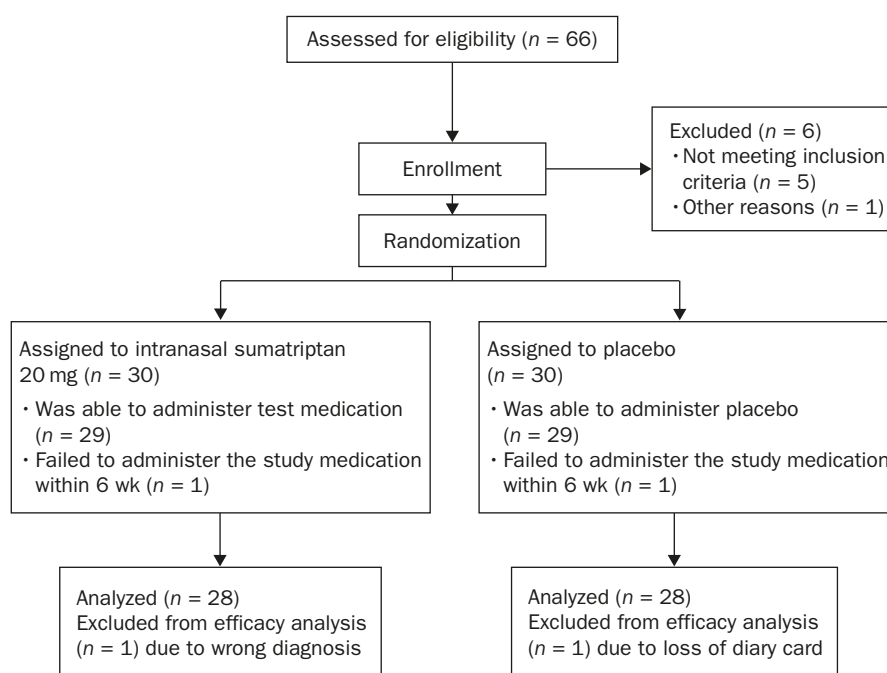
## Results

### *Patient characteristics*

A total of 60 patients were enrolled in the study and randomized to receive treatment with sumatriptan nasal spray or placebo (Figure 1). Among these patients, 4 were withdrawn from the study: 2 from the sumatriptan group and 2 from the placebo group. One patient in the sumatriptan group failed to take the study medication within 6 weeks, which warranted

withdrawal according to the protocol; the other patient was misdiagnosed (headache was secondary to an arteriovenous malformation rupture). In the placebo group, 1 patient failed to take the study medication within 6 weeks while the other patient lost the diary card. The remaining 56 patients who received the study medication and completed the diary record comprised the intent-to-treat cohort. Table 1 shows the demographic data and baseline headache profiles of both groups. The baseline characteristics of the sumatriptan group did not differ significantly from those of the placebo group. Among the 46 subjects who received prophylactic medications, 35 (76%) received atenolol, 17 (46%) amitriptyline, 7 (15%) flunarizine, 2 (4%) imipramine and 1 (2%) valproic acid. The distribution of these medications did not differ between the treatment and placebo groups.

Of the 56 patients, 53 (26 patients in the sumatriptan group and 27 patients in the placebo group) followed the study procedure completely. One patient in the sumatriptan group and another in the placebo group received analgesics prior to administering the study medication during a migraine episode. One patient in the sumatriptan group took rescue medication within 2 hours of receiving the study drug. At the time of administration of the study medication, the sumatriptan group demonstrated a non-significantly higher severe-to-moderate headache intensity ratio than the placebo group, as well as higher frequencies



**Figure 1.** Patient flow through the trial.

**Table 1.** Demographic data and baseline headache characteristics of participants with migraine

	Sumatriptan (n=28)	Placebo (n=28)	p*
Gender (female/male)	26/2	22/6	0.252
Age, yr (mean ± SD)	37.0 ± 10.8	37.4 ± 9.8	0.619
Aura (with/without)	4/24	3/25	1.000
Intensity (severe/moderate)	25/3	24/4	1.000
Duration of migraine history, yr (mean ± SD)	14.1 ± 9.7	12.2 ± 10.4	0.482
Attacks per month (mean ± SD)	2.7 ± 1.4	3.0 ± 1.5	0.399
Use of medications for migraine prevention	22	24	0.485

\*Comparisons between sumatriptan and placebo groups were performed with the t test,  $\chi^2$  test or Fisher's exact test where appropriate.

**Table 2.** Headache characteristics at the time of study medication administration

	Sumatriptan (n=28)	Placebo (n=28)	p*
Headache characteristic, n (%)			
Intensity (severe/moderate)	13/15 (46/54)	8/20 (29/71)	0.168
Nausea	18 (64)	13 (46)	0.179
Vomiting	6 (21)	1 (4)	0.101
Photophobia	16 (57)	9 (32)	0.060
Phonophobia	20 (71)	16 (57)	0.265
Aura	2 (7)	4 (14)	0.669

\*Comparisons between sumatriptan and placebo groups were performed with the  $\chi^2$  test or Fisher's exact test where appropriate.

of associated migraine symptoms (with the exception of aura) (Table 2).

### ***Efficacy***

#### **Headache relief**

One hour after dosing, 61% (17/28) of sumatriptan nasal spray recipients experienced headache relief compared with 43% (12/28) of placebo recipients ( $p=0.181$ ). A significant difference ( $p<0.05$ ) in headache relief rates between the 2 groups was observed as early as 30 minutes postdose (Figure 2). After adjusting for differences in headache severity at the time of treatment administration, and comparing using general linear model analyses, a significant difference in relief rates was also observed at 45 minutes ( $p=0.026$ ). The difference in headache relief rates between groups diminished over time. Two hours after dosing, 60% of sumatriptan nasal spray recipients reported headache relief compared with 54% in the placebo group ( $p=0.671$ ). Furthermore, the sumatriptan group tended to have less use of rescue medication than the placebo group, but the difference failed to achieve statistical significance.

#### **Headache resolution**

The percentages of patients who were completely free of headache at all time intervals are shown in Figure 3. At 90 minutes postdose, patients receiving sumatriptan nasal spray were more likely to achieve complete

headache relief than placebo recipients (29% vs. 7%,  $p=0.036$ ).

#### **Recurrence**

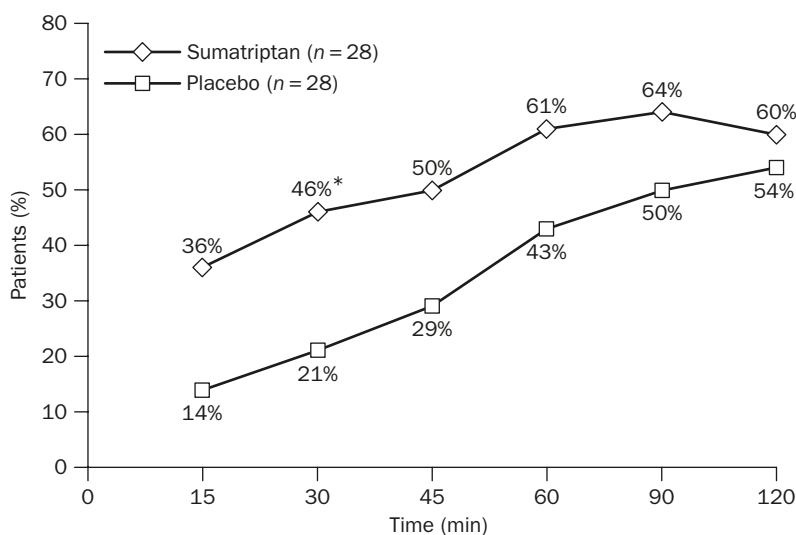
Among those who achieved headache relief after 2 hours, 7 patients experienced recurrence within 24 hours: 3 (19%) in the sumatriptan group and 4 (27%) in the placebo group. Among those who received a second dose for recurrence, 67% (2/3) experienced relief 2 hours after the second dose in the sumatriptan group, while 25% (1/4) experienced relief in the placebo group.

#### **Associated symptoms**

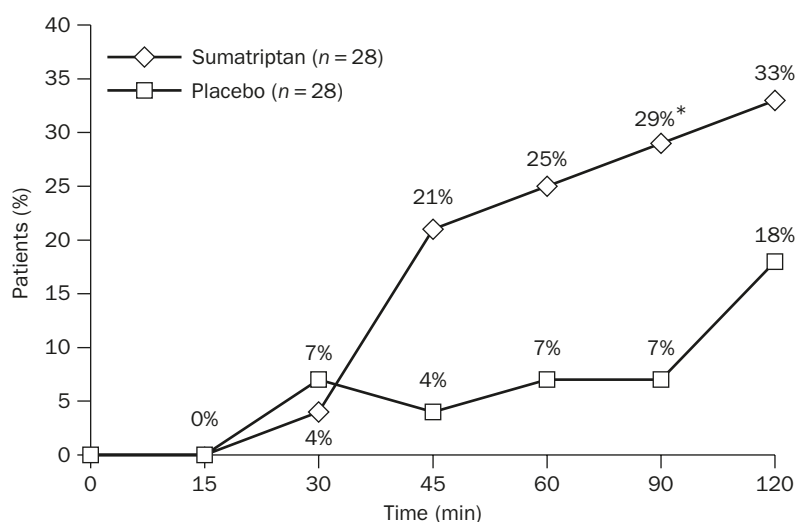
The rates of resolution of nausea, phonophobia and photophobia among those who had these symptoms at the time of initial dosing did not differ between the sumatriptan and placebo recipients. The infrequent occurrence of vomiting in the placebo group ( $n=1$ ) precluded meaningful comparison between the 2 groups.

#### **Time to recovery**

The median time to functional recovery following sumatriptan nasal spray administration was 60 minutes (interquartile range, 125) compared with 209 minutes (interquartile range, 326.25) after placebo (Mann-Whitney test,  $p=0.015$ ). The median times to complete recovery were 175 (interquartile range, 524.5) and



**Figure 2.** Percentage of patients with migraine experiencing headache relief following administration of intranasal sumatriptan or placebo. \* $p < 0.05$  vs. placebo.



**Figure 3.** Percentage of headache-free patients at all time intervals, following intranasal administration of sumatriptan or placebo. \* $p < 0.05$  vs. placebo.

475 minutes (interquartile range, 728.75), respectively, for the 2 groups (Mann-Whitney test,  $p = 0.018$ ).

### Overall rating

A total of 39% of sumatriptan nasal spray recipients and 21% of those treated with placebo rated the study medication as good or excellent for the treatment of migraine ( $p = 0.146$ ).

### Safety and tolerability

Eighty-three percent of the sumatriptan nasal spray group rated the taste of the test medication as unpleasant or very unpleasant. The overall incidence

of patients reporting at least 1 adverse event was 65.5% ( $n = 19$ ) in the sumatriptan nasal spray group and 41.4% ( $n = 12$ ) in the placebo group ( $p = 0.065$ ).

Data from all 58 patients who administered the study medication were used in evaluating adverse events. These adverse events were mostly mild and transient, and none were considered serious. The most commonly reported sumatriptan-related adverse event was bitter taste (21%) (Table 3). With the exception of taste disturbance, the adverse event profile of sumatriptan nasal spray was similar to that of placebo. Only 1 patient in the sumatriptan nasal spray group complained of chest tightness.

**Table 3.** Summary of reported adverse events in participants following administration of intranasal sumatriptan or placebo

	Sumatriptan (n = 29)	Placebo (n = 29)
Bitter taste	6	0
Vomiting*	4	1
Nasal discomfort	4	0
Worsening of headache	2	0
Muscle soreness	2	0
Dizziness	1	2
Weakness	1	1
Palpitations	1	1
Throat discomfort	1	1
Anxiety	0	2
Photosensitivity	1	0
Chest tightness	1	0
Epigastric pain	1	0
Diarrhea	1	0
Wet nostrils	1	0
Nasal stuffiness	1	0
Difficulty opening mouth	1	0
Syncopal attack	1	0
Fatigue	1	0
Chills	1	0
Sweating	1	0
Tremors	1	0
Cough	1	0
Bone pain	1	0
Allergy	1	0
Toothache	1	0
Scalp numbness	1	0
Nausea	0	1
Insomnia	0	1
Flushing	0	1
Tonsil inflammation	0	1
Vocal cord inflammation	0	1
Heat sensation in throat	0	1
Swelling of the head	0	1
Total number of patients reporting adverse events	19	12

\*Including vomiting due to bitter taste.

## Discussion

The results of this randomized double-blind, placebo-controlled trial demonstrated that sumatriptan 20-mg nasal spray is a rapidly effective and well-tolerated treatment for patients with acute migraine attacks. After 60 minutes, 61% of patients treated with sumatriptan nasal spray experienced headache relief. A significant difference from the effects of treatment with placebo was observed at 30 minutes. Nausea, photophobia and phonophobia were alleviated in the majority of patients

in the sumatriptan nasal spray group, although the benefit in comparison to placebo did not reach statistical significance. Most of the adverse events reported in the sumatriptan group were mild and transient, and none were considered serious.

The demographic data and baseline headache characteristics of the 2 treatment groups were similar upon enrollment into the trial, indicating successful randomization. However, the headache profile of patients at the time of drug administration seemed to be more severe in sumatriptan recipients, probably because of the small sample size. After adjustment for headache severity at the time of drug administration, a significant difference in relief rates between groups was also observed at 45 minutes postdose.

With respect to response rates following sumatriptan nasal spray administration, the results of this study were similar to those of 2 large-scale, randomized, placebo-controlled clinical trials conducted in the United States (46–48% in 60 minutes, 62–63% in 120 minutes).<sup>9</sup> This was also the case with response rates, in terms of headache relief, headache elimination, and improvement of nausea, photophobia and phonophobia, reported in a review of 5 large-scale trials, the US trials included.<sup>10</sup> A retrospective analysis of intranasal sumatriptan trials demonstrated that headache relief rates from intranasal sumatriptan were not affected in a clinically significant way by race.<sup>5</sup> With the current scarcity of Asian data concerning the clinical use of intranasal sumatriptan, the present study may serve as a reference for future Asian triptan studies.

Despite the high response rates observed in the active arm of the present study, the benefits of sumatriptan nasal spray treatment over placebo failed to reach statistical significance in several efficacy parameters. This may be partly due to the high efficacy rates observed in the group treated with placebo. However, the small sample size in this study should also be taken into consideration. A review showed that in pain trials, treatment with placebo produced a standard mean difference of 27% (95% confidence interval, 15–40%) when compared with no treatment.<sup>11</sup> In previous placebo-controlled intranasal sumatriptan trials largely conducted in Western populations, the relief rates with placebo were 30% at 1 hour and 25–36% at 2 hours.<sup>4,9,10</sup> In the present study, however, the placebo group demonstrated headache relief rates of 43% at 1 hour and 54% at 2 hours. A similar phenomenon was observed in another Asian oral triptan trial. In a Japanese trial investigating eletriptan for migraine, the placebo group reported a 51% headache response rate at 2 hours, whereas placebo response rates in Western eletriptan trials were from 22% to 24%.<sup>12</sup> The reason for the



higher placebo response in the present study was unclear, although lower headache severity in the placebo group compared with the sumatriptan group may be a factor. Previous triptan exposure may also influence placebo response, but this was not accounted for in the present study. The magnitude of pain relief from placebo is strongly associated with expectancy of pain relief, conditioning, and whether analgesia was assessed concurrently or retrospectively, hence suggesting a psychologic aspect to the placebo effect.<sup>12,13</sup> With high placebo rates observed in both the present study and the Japanese eletriptan trial,<sup>6</sup> a relation between ethnicity and the magnitude of the placebo effect may be surmised and should be a focus of investigation. A review on placebo responses in oral triptan trials indicate that geographic location does not significantly account for placebo response, but this review only compared North American trials with European trials.<sup>14</sup> However, the study did demonstrate a wide variability in placebo response rates (range, 17–50%). This supports the premise that placebo response may be influenced by several factors. Together with the high placebo rate in the present trial, this highlights the importance of recruiting a placebo group in acute migraine trials.<sup>15</sup>

After intranasal administration, sumatriptan is directly and rapidly absorbed, with 60% of the maximum plasma concentration ( $C_{max}$ ) occurring at 30 minutes after administration of a single 20 mg dose. Sumatriptan is bound to plasma proteins to a low extent, 14–21%. Sumatriptan is cleared predominately through metabolism by monoamine oxidase enzymes.<sup>16</sup> Its major metabolite, an indoleacetic analog, has no 5-HT<sub>1</sub> activity. Pharmacokinetics of oral or subcutaneous sumatriptan are not affected by ethyl alcohol, dihydroergotamine, propranolol, flunarizine, pizotifen, butorphanol, clarithromycin, ethinylestradiol and norethindrone, by the “second-generation” triptans such as alniditan or naratriptan, or by the selective serotonin reuptake inhibitor paroxetine, to a clinically significant extent.<sup>17</sup> Because MAO-A inhibitors can increase plasma concentration of sumatriptan, they were contraindicated in this trial. Although the percentage of patients on preventive medications was high in this study, the drug-drug interaction might not play a role in the evaluation of the efficacy of intranasal sumatriptan.

In line with a previous review of sumatriptan intranasal studies,<sup>10</sup> taste disturbance, vomiting and nasal discomfort were the 3 most common adverse events in sumatriptan recipients. Taste disturbance was expectedly the most commonly reported adverse experience with intranasal sumatriptan, but this may be of relatively minor importance since previous studies have reported that patients consider taste to be unimportant in the

choice of an antimigraine medication.<sup>10</sup> It is likely that certain potentially drug-related events, such as vomiting and worsening of headaches, may be symptoms of migraine attack itself. The frequencies of nausea or vomiting and nasal discomfort in our study were 13.8% and 13.8%, respectively; whereas those in a review of 5 clinical trials were 13.5% for nausea and vomiting and 3.8% for nasal discomfort.<sup>18</sup> However, it is difficult to make meaningful comparisons of these 2 adverse events since the number of subjects in the study was small. Nevertheless, the trend is similar to the results of other international studies. Although none of the patients who received placebo reported taste disturbance, 41% reported at least 1 adverse event. This figure is higher than those reported by placebo groups in other studies.<sup>19</sup> Most of the reported adverse events in the placebo group were features associated with migraine attacks or anxiety.

## Acknowledgments

This study was supported by a grant from Glaxo-SmithKline Far East B.V. Taiwan Branch.

## References

1. Wang SJ. Epidemiology of migraine and other types of headache in Asia. *Curr Neurol Neurosci Rep* 2003;3:104–8.
2. Wang SJ, Fuh JL, Young YH, Lu SR, Shia BC. Prevalence of migraine in Taipei, Taiwan: a population-based survey. *Cephalalgia* 2000;20:566–72.
3. Rapoport AM, Tepper SJ, Bigal ME, Sheftell FD. The triptan formulations: how to match patients and products. *CNS Drugs* 2003;17:431–47.
4. Salonen R, Ashford E, Dahlof C, Dawson R, Gilhus NE, Luben V, Noronha D, et al. Intranasal sumatriptan for the acute treatment of migraine. International Intranasal Sumatriptan Study Group. *J Neurol* 1994;241:463–9.
5. Ashford E, Salonen R, Saiers J, Woessner M. Consistency of response to sumatriptan nasal spray across patient subgroups and migraine types. *Cephalalgia* 1998;18:273–7.
6. Eletriptan Steering Committee in Japan. Efficacy and safety of eletriptan 20 mg, 40 mg and 80 mg in Japanese migraineurs. *Cephalalgia* 2002;22:416–23.
7. Headache Classification Committee of the International Headache Society. Classification and diagnostic criteria for headache disorders, cranial neuralgias and facial pain. *Cephalalgia* 1988; 8:1–96.
8. Havanka H, Dahlof C, Pop PH, Diener HC, Winter P, Whitehouse H, Hassani H. Efficacy of naratriptan tablets in the acute treatment of migraine: a dose-ranging study. Naratriptan S2WB2004 Study Group. *Clin Ther* 2000;22: 970–80.
9. Ryan R, Elkind A, Baker CC, Mullican W, DeBussey S, Asgharnejad M. Sumatriptan nasal spray for the acute treatment of migraine: results of two clinical studies. *Neurology* 1997; 49:1225–30.

10. Dahlof C. Sumatriptan nasal spray in the acute treatment of migraine: a review of clinical studies. *Cephalalgia* 1999;19:769–78.
11. Hrobjartsson A, Gotzsche PC. Is the placebo powerless? An analysis of clinical trials comparing placebo with no treatment. *N Engl J Med* 2001;344:1594–602.
12. Sakai F, Diener HC, Ryan R, Poole P. Eletriptan for the acute treatment of migraine: results of bridging a Japanese study to Western clinical trials. *Curr Med Res Opin* 2004;20:269–77.
13. Price DD, Milling LS, Kirsch I, Duff A, Montgomery GH, Nicholls SS. An analysis of factors that contribute to the magnitude of placebo analgesia in an experimental paradigm. *Pain* 1999;83:147–56.
14. Loder E, Goldstein R, Biondi D. Placebo effects in oral triptan trials: the scientific and ethical rationale for continued use of placebo controls. *Cephalalgia* 2005;25:124–31.
15. Diener HC. Placebo in headache trials. *Cephalalgia* 2003;23:485–6.
16. Moore KHP, Hussey EK, Shaw S, Fuseau E, Duquesnoy C, Pakes GE. Safety, tolerability, and pharmacokinetics of sumatriptan in healthy subjects following ascending single intranasal doses and multiple intranasal doses. *Cephalalgia* 1997;17:541–50.
17. Fuseau E, Petricoul O, Moore KHP, Barrow A, Ibbotson T. Clinical pharmacokinetics of intranasal sumatriptan. *Clin Pharmacokinet* 2002;41:801–11.
18. Rapoport A. The sumatriptan nasal spray: a review of clinical trials. *Cephalalgia* 2001;21:13–5.
19. Reuter U, Sanchez del Rio M, Carpay JA, Boes CJ, Silberstein SD, GSK Headache Masters Program. Placebo adverse events in headache trials: headache as an adverse event of placebo. *Cephalalgia* 2003;23:496–503.