Original Paper

European Neurology

Eur Neurol 2003;49:20–29
DOI: 10.1159/000067018

Received: March 13, 2002
Accepted: September 10, 2002

# Crossover Comparison of Efficacy and Preference for Rizatriptan 10 mg versus Ergotamine/Caffeine in Migraine

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Key Words
Rizatriptan · Ergotamine · Efficacy · Preference · Migraine

Abstract
Rizatriptan is a selective 5-$HT_{1B/1D}$ receptor agonist with rapid oral absorption and early onset of action in the acute treatment of migraine. This randomized double-blind crossover outpatient study assessed the preference for 1 rizatriptan 10 mg tablet to 2 ergotamine 1 mg/caffeine 100 mg tablets in 439 patients treating a single migraine attack with each therapy. Of patients expressing a preference (89.1%), more than twice as many preferred rizatriptan to ergotamine/caffeine (69.9 vs. 30.1%, $p \leq 0.001$). Faster relief of headache was the most important reason for preference, cited by 67.3% of patients preferring rizatriptan and 54.2% of patients who preferred ergotamine/caffeine. The co-primary endpoint of being pain free at 2 h was also in favor of rizatriptan. Forty-nine percent of patients were pain free 2 h after rizatriptan, compared with 24.3% treated with ergotamine/caffeine ($p \leq 0.001$), rizatriptan being superior within 1 h of treatment. Headache relief at 2 h was 75.9% for rizatriptan and 47.3% for ergotamine/caffeine ($p \leq 0.001$), with rizatriptan being superior to ergotamine/caffeine within 30 min of dosing. Almost 36% of patients taking rizatriptan were pain free at 2 h and had no recurrence or need for additional medication within 24 h, compared to 20% of patients on ergotamine/caffeine ($p \leq 0.001$). Rizatriptan was also superior to ergotamine/caffeine in the proportions of patients with no nausea, vomiting, phonophobia or photophobia and for patients with normal function 2 h after drug intake ($p \leq 0.001$). More patients were (completely, very or somewhat) satisfied 2 h after treatment with rizatriptan (69.8%) than at 2 h

S.C. takes full responsibility for the data, the analyses and interpretation, and the conduct of the research. She had full access to the study data and had the right to publish any and all of the data, separate and apart from the attitudes of the sponsor.

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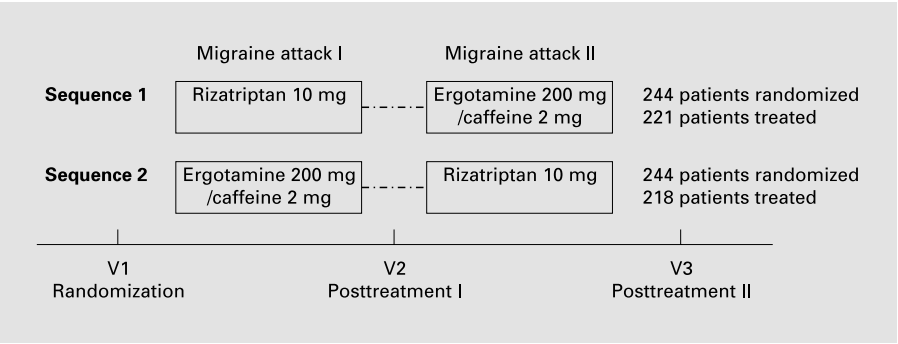


Fig. 1. Study design.

after treatment with ergotamine/caffeine (38.6%, $p \leq 0.001$). Recurrence rates were 31.4% with rizatriptan and 15.3% with ergotamine/caffeine. Both active treatments were well tolerated. The most common adverse events (incidence ≥5% in one group) after rizatriptan and ergotamine/caffeine, respectively, were dizziness (6.7 and 5.3%), nausea (4.2 and 8.5%) and somnolence (5.5 and 2.3%).



## Introduction

Rizatriptan is a 5-$HT_{1B/1D}$ receptor agonist used for the acute treatment of migraine at oral doses of 5 and 10 mg. In clinical studies, both doses were shown to be highly effective compared to placebo, with the 10-mg dose providing headache relief as early as 30 min after dosing, and were well tolerated [1]. Rizatriptan 10 mg was more effective than rizatriptan 5 mg with respect to headache relief, freedom from pain and associated migraine symptoms, as well as return to normal function and the need for additional medication [2].

Ergotamine is a traditional therapy for migraine and is widely available. Ergotamine is usually combined with caffeine, which enhances absorption [3, 4]. The 2-mg dose of ergotamine is the middle of the recommended oral dose range [5] and has tolerability data available from previous studies [6, 7]. Direct comparator studies are useful in helping physicians select the most appropriate therapy for a patient. Furthermore, preference is a patient-focused composite endpoint, which incorporates the efficacy, tolerability and formulation of a medicine. The study described below was thus conducted to assess the efficacy and preference for rizatriptan 10 mg compared to ergotamine 2 mg/caffeine 200 mg.

## Methods

*Patients*

A total of 488 women and men from 11 countries who met International Headache Society criteria for migraine [8] with or without aura were enrolled. Patients had to have a 6-month history of migraine and usually experienced 1–8 attacks per month. Patients were excluded if they had clinical evidence of cerebrovascular or cardiovascular disease, including significant ECG abnormality, or if they had a history within 1 year or current evidence of drug or alcohol abuse. Patients with any contraindication or sensitivity to 5-$HT_{1B/1D}$ agonists or those who had received treatment with any other investigational compound or device within the past 30 days were also excluded, as were pregnant women or nursing mothers.

Approvals were obtained from local regulatory authorities and Ethical Review Committees, and each patient who participated in the trial gave written informed consent. The study conformed to Good Clinical Research Practice.

*Study Design and Procedure*

This randomized, double-blind, double-dummy, crossover outpatient study compared the clinical profiles of a rizatriptan tablet to ergotamine/caffeine tablets for the acute treatment of a single migraine attack with each agent. The study was conducted at 41 international sites. The randomization schedule was generated using a random number generator in SAS® statistical analysis software version 8.1. Providing patients with rizatriptan, ergotamine/caffeine and matching placebo depending on the sequence ensured blinding. Patients were randomized to one of the two sequences in a 1:1 ratio. In sequence 1, patients treated their first migraine attack with 1 rizatriptan 10 mg tablet and their second attack with 2 ergotamine 1 mg/caffeine 100 mg tablets. In sequence 2, patients did the reverse: the first migraine attack was treated with 2 ergotamine 1 mg/caffeine 100 mg tablets and the second attack with 1 rizatriptan 10 mg tablet (fig. 1). For each attack, patients took a single dose of study medication for a migraine headache that was not resolving spontaneously and was of moderate or severe intensity on a 4-point headache severity scale (0 = none, 1 = mild, 2 = moderate, 3 = severe), provided that they had not taken any prohibited medications (monoamine oxidase inhibitors or methysergide within the past 2 weeks; ergotamine/caffeine within the past 4 days, any triptan or opiate within the past 24 h and any other analgesic or antiemetic within the past 6 h). Propranolol use within the last 3 days was also prohibited, because rizatriptan

5 mg is the recommended dose in patients taking concomitant propranolol. Other migraine prophylaxis was permitted. Nonresponders, whose headaches failed to improve to grade 0 or 1 (absent or mild) at 2 h after dose, were permitted optional additional analgesia (e.g. nonsteroidal anti-inflammatory drugs or opiates) and/or antiemetics. Patients with headache relief at 2 h (reduction in severity from grade 2 or 3 at baseline to grade 0 or 1) who then experienced recurrent headache (return to grade 2 or 3) within 24 h of initial dosing could take a further dose of the same study medication. Any further headache recurrence within the attack was treated with additional analgesics or antiemetics. Female patients recorded the onset date of their last menstrual period as appropriate, to allow assessment of consistency of treatment effect across menstrually/nonmenstrually associated migraine attacks (menstrually associated migraine attack defined as occurring within –3 to +3 days of the onset date of the last menstrual period).

At the posttreatment visit following treatment of the second attack, patients completed the Patient Preference Question, namely: 'If you had to treat your migraine headache with one of these two headache medications, would you prefer the treatment I or the treatment II?' (I prefer taking treatment I; I prefer taking treatment II; I have no preference). If patients stated a preference, they were then given a list of reasons and specified the one most important reason for preferring one treatment to the other (table 1). The reasons were randomly ordered and included efficacy and tolerability topics. All questions had content validity established by testing within a migraine patient population, using a standardized development method [9].

*Outcome Measures*

At baseline and at 0.5, 1, 1.5 and 2 h after dosing, the patients rated their headache severity in a diary using the 4-grade scale described above. A number of parameters were derived from this scale for analysis:

(1) headache relief: the reduction of headache severity from grade 2 or 3 at baseline to grade 0 or 1;

(2) time to headache relief within 2 h: the first time (0.5, 1, 1.5 or 2 h) that a patient reported headache relief in the 2 h after dosing;

(3) being pain free: the complete abolition of headache (grade 0);

(4) time to being pain free within 2 h: the first time (0.5, 1, 1.5 or 2 h) that a patient reported the complete abolition of headache in the 2 h after dosing.

Patients also recorded their functional disability (0 = normal, 1 = mildly impaired, 2 = severely impaired, 3 = unable to do activities, requires bedrest) and the presence or absence of associated symptoms (nausea, vomiting, photophobia and phonophobia) at the same time points as the ratings of headache severity. From these data, freedom from pain and associated symptoms at 2 h was calculated, which was defined as no headache, no nausea, no vomiting, no photophobia, no phonophobia and no functional disability 2 h after intake. At 2 h after dose, patients recorded their satisfaction with the study medication (1 = completely satisfied, couldn't be better; 2 = very satisfied; 3 = somewhat satisfied; 4 = neither satisfied nor dissatisfied; 5 = somewhat dissatisfied; 6 = very dissatisfied; 7 = completely dissatisfied, couldn't be worse). The use of additional analgesics/antiemetics taken from 2 to 24 h was recorded, as well as the time and maximum severity of any headache recurrence. From these data, the sustained pain-free (respectively headache relief) responses over 24 h after dosing were calculated. A sustained pain-free (respectively headache relief) response was defined as being pain free (respectively headache relief) at 2 h, with no need for additional medication and no headache recurrence during 2–24 h after dosing with the study medication.

Table 1. Reasons for preference

| | |
|---|---|
| a | Treatment I relieved my headache faster than treatment II |
| b | Treatment I relieved my nausea faster than treatment II |
| c | I returned to my normal activities more quickly with treatment I than with treatment II |
| d | I had fewer side effects with treatment I than with treatment II |
| e | The headache came back with treatment II, but not with treatment I |
| f | Treatment II made my nausea worse |
| g | Treatment I relieved my sensitivity to light or sound faster than treatment II |
| h | Other reasons |

For patients who stated they preferred treatment I to treatment II (or vice versa).

*Sample Size Calculations*

The sample size of this study was based on the co-primary efficacy hypotheses that patients would (i) demonstrate a greater preference for the rizatriptan tablet versus ergotamine/caffeine tablets or (ii) rizatriptan would be superior to ergotamine/caffeine in the proportion of patients pain free at 2 h. A total of 372 evaluable patients (186 per sequence) was required to have approximately 95% power to detect a 20% point difference in preference (60 vs. 40%) for rizatriptan compared to ergotamine/caffeine (using a significance level of 0.025 to adjust for the two primary hypotheses). The result was computed based on the binomial distribution (null hypothesis p = 50% versus alternative hypothesis p = 60%).

Based on published data [1, 6, 7], it was assumed that rizatriptan 10 mg and ergotamine/caffeine would render approximately 40 and 10–13% of patients pain free at 2 h, respectively. The power to detect this difference in pain-free rates was above 99%. Approximately 450 patients had to be randomized (225 by sequence) to account for dropouts and respondents with no preference.

*Statistical Analyses*

All statistical analyses were performed by MSD, using SAS version 8.1. The co-primary efficacy analysis of the preference was based on all patients who treated both attacks and expressed a preference for one medication over the other. The Mainland-Gart procedure [10] was used to compare the number of patients preferring a rizatriptan tablet to the number of patients preferring ergotamine/caffeine tablets. A post hoc analysis to include the patients who did not express a preference was performed with the Prescott test [10]. This test is an alternative to the Mainland-Gart test but does not discard any information from patients with no preference.

The co-primary efficacy analysis of being pain free at 2 h and secondary efficacy analyses were based on the 'intention-to-treat' approach, including all patients who took at least one dose of study medication and recorded at least one efficacy rating after dosing. In this approach, missing data at a particular time point in a treatment period were estimated by carrying forward the preceding data in that

Table 2. Patient accounting in the study

| | Sequence 1: rizatriptan 10 mg/ergotamine 2 mg + caffeine 200 mg | | Sequence 2: ergotamine 2 mg + caffeine 200 mg/rizatriptan 10 mg | | Total | |
|---|---|---|---|---|---|---|
| | n | % | n | % | n | % |
| Patients randomized | 244 | | 244 | | 488 | |
| Not treated | 23 | 9.4 | 26 | 10.7 | 49 | 10.0 |
| Treated | 221 | 90.6 | 218 | 89.3 | 439 | 90.0 |
| Patients treated | 221 | | 218 | | 439 | |
| Patients completed study | 182 | 82.4 | 180 | 82.6 | 362 | 82.5 |
| Total discontinued (after attack I) | 39 | 17.6 | 38 | 17.4 | 77 | 17.5 |
| Clinical AE | 3 | 1.4 | 0 | 0.0 | 3 | 0.7 |
| Lack of efficacy | 2 | 0.9 | 2 | 0.9 | 4 | 0.9 |
| Lost to follow-up | 0 | 0.0 | 1 | 0.5 | 1 | 0.2 |
| Patient moved | 0 | 0.0 | 1 | 0.5 | 1 | 0.2 |
| Patient withdrew consent | 3 | 1.4 | 2 | 0.9 | 5 | 1.1 |
| Protocol deviation | 4 | 1.8 | 7 | 3.2 | 11 | 2.5 |
| Patient discontinued for other reason[1] | 27 | 12.2 | 25 | 11.5 | 52 | 11.8 |
| Patients not treated | 23 | | 26 | | 49 | |
| Clinical AE | 1 | 4.3 | 0 | 0.0 | 1 | 2.0 |
| Lost to follow-up | 0 | 0.0 | 3 | 11.5 | 3 | 6.1 |
| Patient withdrew consent | 4 | 17.4 | 4 | 15.4 | 8 | 16.3 |
| Protocol deviation | 1 | 4.3 | 3 | 11.5 | 4 | 8.2 |
| Patient discontinued for other reason[1] | 17 | 73.9 | 16 | 61.5 | 33 | 67.3 |

[1] The majority of these patients discontinued because they had no migraine attack within 2 months.

treatment period. However, baseline data were not used for imputation and were not 'carried forward'.

Percentages of patients with headache relief, pain freedom, associated symptoms, functional disability and who took additional medication were analyzed with logistic regression using the generalized estimating equations (GEE) methodology to account for intrasubject correlations. This regression was performed using SAS 8.1, with the GENMOD (generalized linear model) procedure. The main model included factors for treatment, period, geographical region and baseline headache severity. The 7 scores of satisfaction with medication at 2 h after dose were dichotomized into score 1, 2, 3 versus score 4, 5, 6, 7 and analyzed with logistic regression, using the same model as described above.

In the time to headache relief (respectively pain freedom) analysis, patients were considered censored either at 2 h, if their headache severity was still moderate or severe (respectively mild, moderate or severe) up to 2 h, or at an earlier time, if headache relief (pain freedom) was not yet achieved and followed by missing pain severity up to 2 h. The 'time to' analysis used data from all time points to define the likelihood of headache relief (pain freedom) following treatment through the entire assessment period [11]. A binary regression model adapted to the analysis of interval censored data was used for the comparisons of headache relief (pain freedom). To account for the intrasubject correlations, the GEE method was used. The main model included factors for treatment, baseline headache severity, time interval, period and geographical region.

For all efficacy endpoints, consistency of the treatment effect across geographical region, baseline headache severity and effect of the sequence group were assessed, via the appropriate main factors or interactions in the models described above.

Treatment effects were quantified by means, percentages, hazard ratios or odds ratios as appropriate. As there were two co-primary endpoints, a multiplicity adjustment was planned using Hochberg's procedure. The overall type I error was set at $\alpha = 0.05$.

All patients who took study medication were included in the safety analyses, the primary endpoint of which was the overall incidence of adverse events. Primary comparisons of treatment were based on the McNemar test and secondary analyses were based on logistic regression with the GEE approach. A 'newly emergent' approach was taken for the analysis of adverse events. That is, adverse events, which continued from the first period of the crossover to the second period, were only counted against the treatment on which they arose.

## Results

### *Study Population*

A total of 488 patients were randomized to one of the two treatment sequences (table 2). Of those randomized, 49 did not take study medication, the primary reason being lack of migraine headache during the study period. Of the 439 patients treated, 362 completed the study and

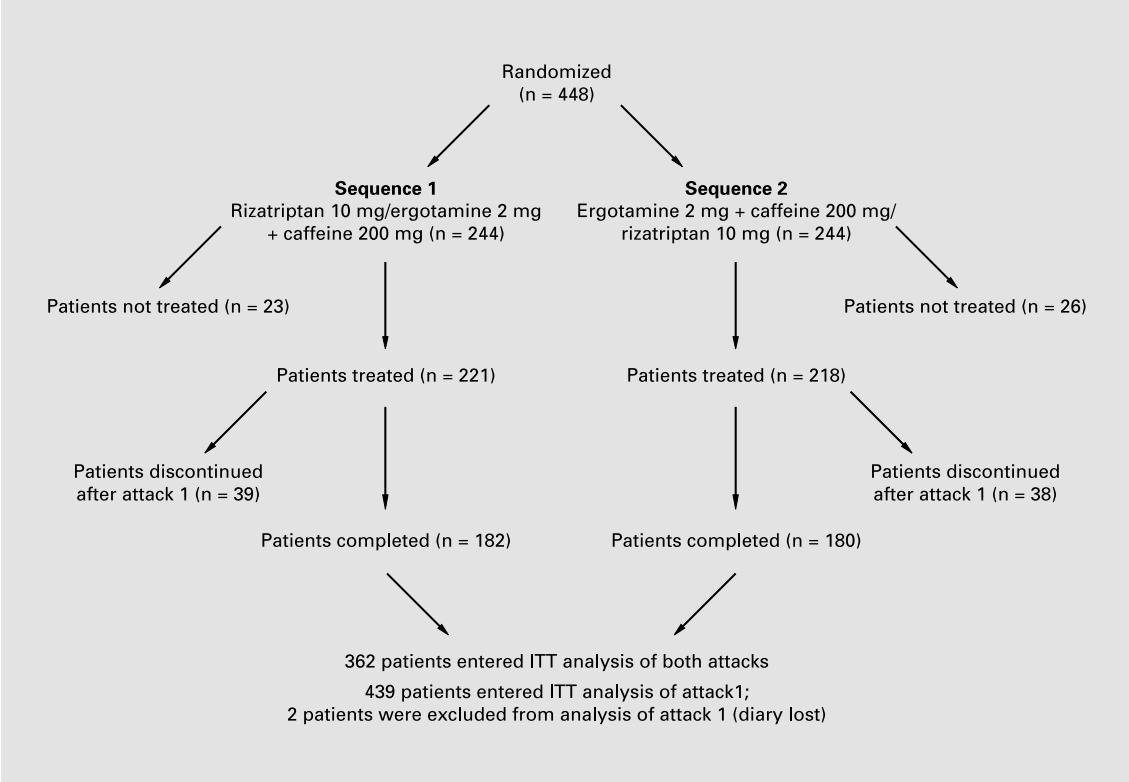


Fig. 2. Study flow diagram. ITT = Intention to treat.

treated both attacks. Seventy-seven patients discontinued before the second treatment (also mainly because of lack of migraine during this period). Three patients initially treated with rizatriptan discontinued due to an adverse event (AE); one of those was a serious AE described below. The study flow is detailed in figure 2 and the reasons for discontinuation described in table 2.

The groups that were randomized to treat either with rizatriptan or ergotamine/caffeine initially were similar with regard to age, sex, race, baseline headache severity, presence of aura, use of migraine prophylaxis and use of oral contraception in women (table 3). Almost 20% of patients recorded a family history of diabetes, 10.5% a family history of cardiovascular disease and 22.3% were current smokers.

## *Efficacy*

### *Headache Relief and Being Pain Free up to 2 h*

The proportions of patients who reported headache relief and being pain free at time points up to 2 h are shown in figures 3 and 4, respectively. Headache relief at 2 h was 75.9% for rizatriptan and 47.3% for ergotamine/caffeine ($p \leq 0.001$), with rizatriptan being superior to ergotamine/caffeine within 30 min after dosing. Forty-nine percent of patients were pain free 2 h after rizatriptan (the co-primary efficacy endpoint), compared to 24.3% treated with ergotamine/caffeine [odds ratio and 95% confidence interval, CI, 3.07 (2.27, 4.16), $p \leq 0.001$] and rizatriptan was superior within 1 h of treatment.

### *Preference*

Of the 358 patients who completed the preference questionnaire, 39 patients (10.9%) did not express a preference for one of the two treatments. Of the 319 patients who did express a preference (co-primary study endpoint), 223 patients (69.9%) preferred rizatriptan and 96 patients (30.1%) preferred ergotamine/caffeine ($p \leq 0.001$). When the patients who did not express a preference were accounted for, rizatriptan was still preferred over ergotamine/caffeine (62.3 vs. 26.8%, respectively, $p \leq 0.001$). The p value for the period effect was significant ($p = 0.002$), as the preference for the second period

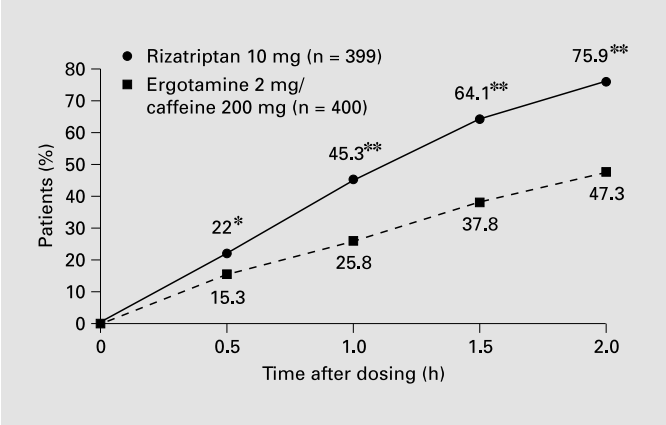


Fig. 3. Percentages of patients who reported headache relief in the 2-hour interval following dosing. * p = 0.024, ** p ≤ 0.001 versus ergotamine/caffeine.

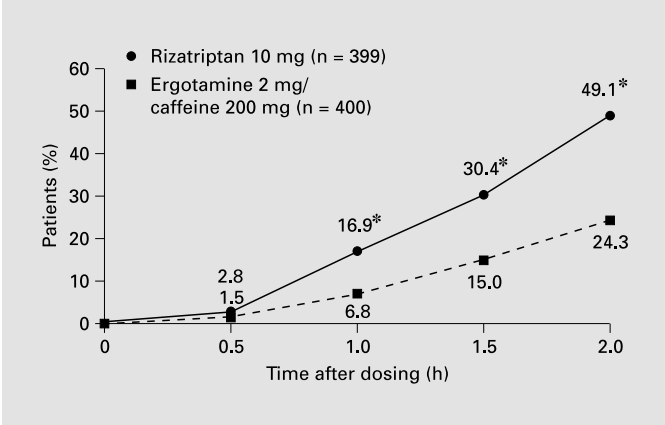


Fig. 4. Percentages of patients who reported freedom from pain in the 2-hour interval following dosing. * p ≤ 0.001 versus ergotamine/caffeine.

Table 3. Patient baseline characteristics

| | Sequence 1: rizatriptan 10 mg/ergotamine 2 mg + caffeine 200 mg (n = 221) | | Sequence 2: ergotamine 2 mg + caffeine 200 mg/rizatriptan 10 mg (n = 218) | | Total (n = 439) | |
|---|---|---|---|---|---|---|
| | n | % | n | % | n | % |
| Gender | | | | | | |
| Female | 182 | 82.4 | 184 | 84.4 | 366 | 83.4 |
| Male | 39 | 17.6 | 34 | 15.6 | 73 | 16.6 |
| Age, years | | | | | | |
| Mean | 37.6 | | 36.9 | | 37.2 | |
| Range | 18–70 | | 18–62 | | 18–70 | |
| Racial origin | | | | | | |
| Caucasian | 166 | 75.1 | 169 | 77.5 | 335 | 76.3 |
| Hispanic | 45 | 20.4 | 41 | 18.8 | 86 | 19.6 |
| Other | 10 | 4.5 | 8 | 3.7 | 18 | 4.1 |
| Family history | | | | | | |
| Diabetes requiring drug therapy | 49 | 22.2 | 37 | 17.0 | 86 | 19.6 |
| Cardiovascular disease | 23 | 10.4 | 23 | 10.6 | 46 | 10.5 |
| Tobacco use | | | | | | |
| Current smoker | 46 | 20.8 | 52 | 23.9 | 98 | 22.3 |
| Ex or no smoker | 175 | 79.2 | 166 | 76.1 | 341 | 77.7 |
| Baseline severity[1] | | | | | | |
| Missing information | 0 | 0.0 | 1 | 0.5 | 1 | 0.2 |
| Moderate migraine | 122 | 55.7 | 110 | 50.5 | 232 | 53.1 |
| Severe migraine | 97 | 44.3 | 107 | 49.1 | 204 | 46.7 |
| Presence of aura[1] | 33 | 14.9 | 32 | 14.7 | 65 | 14.8 |
| Menstrually associated[1,2] | 51 | 28.0 | 34 | 18.5 | 85 | 23.2 |
| Used prophylaxis | 48 | 21.7 | 37 | 17.0 | 85 | 19.4 |
| Used oral contraception[2] | 38 | 20.9 | 31 | 16.8 | 9 | 18.9 |

[1] First attack.
[2] Percentages were calculated based on women only.

Table 4. Secondary efficacy measures

| Outcome measure | Rizatriptan 10 mg | | Ergotamine 2 mg + caffeine 200 mg | |
|---|---|---|---|---|
| | n/total | % | n/total | % |
| Functioning normally[1] | | | | |
| At 0 h | 16/398 | 4.0 | 23/395 | 5.8 |
| At 2 h | 226/399 | 56.6* | 111/399 | 27.8 |
| Without nausea | | | | |
| At 0 h | 185/399 | 46.4 | 166/398 | 41.7 |
| At 2 h | 330/399 | 82.7* | 225/400 | 56.3 |
| Without vomiting | | | | |
| At 0 h | 367/399 | 92.0 | 366/398 | 92.0 |
| At 2 h | 384/399 | 96.2* | 358/400 | 89.5 |
| Without photophobia | | | | |
| At 0 h | 102/399 | 25.6 | 94/398 | 23.6 |
| At 2 h | 285/399 | 71.4* | 200/400 | 50.0 |
| Without phonophobia | | | | |
| At 0 h | 132/399 | 33.1 | 127/398 | 31.9 |
| At 2 h | 314/399 | 78.7* | 219/400 | 54.8 |
| Need for additional medication after 2–24 h | 111/401 | 27.7* | 182/400 | 45.5 |
| Completely or very satisfied with medication at 2 h | 174/397 | 43.8* | 85/394 | 21.6 |

* $p \leq 0.001$ versus ergotamine/caffeine.

[1] Treatment comparisons were based on a comparison of normal function versus functionally disabled states.

was higher than the preference for the first period (independently of the treatment preferred, 41.7% of the patients expressed a preference for the first period while 58.3% preferred the treatment used for their second migraine attack). The presence of such an effect implies a higher preference rate for rizatriptan in sequence 2 (preference for rizatriptan was 78.1%, when it was taken to treat the second migraine attack) than in sequence 1 (preference for rizatriptan was 61.6%, when it was taken to treat the first migraine attack). Faster relief of headache was the most important reason for preference, cited by 67.3% of patients preferring rizatriptan and 54.2% of patients who preferred ergotamine/caffeine. This was followed by 8.5% of patients stating that they returned to their normal activities quicker with rizatriptan, compared to 21.9% of patients who preferred ergotamine/caffeine on these grounds, and 6.7% citing fewer side effects with rizatriptan as their reason for preference (compared to 4.2% of patients who preferred ergotamine/caffeine on this point).

*Time to Headache Relief and Time to Pain Freedom up to 2 h*

The rizatriptan 10 mg tablet was significantly superior to ergotamine/caffeine with respect to time to headache relief ($p \leq 0.001$). The hazard ratio was 2.05 (95% CI 1.72, 2.44). This means that at any time in the 2-hour period, headache in a patient on rizatriptan was more than twice as likely to be relieved within the next few minutes than in a patient taking ergotamine/caffeine. In addition, a patient was more than twice as likely to become pain free sooner with rizatriptan than with ergotamine/caffeine, the pain free hazard ratio being 2.45 (95% CI 1.93, 3.10, $p \leq 0.001$).

*Associated Symptoms*

The proportions of patients without associated migraine symptoms of nausea, vomiting, photophobia and phonophobia at 0 and 2 h are summarized in table 4. Rizatriptan was superior to ergotamine/caffeine in the proportion of patients with no nausea from 30 min onwards. At 2 h, the proportions of patients with no nausea were 82.7% after rizatriptan and 56.2% following

ergotamine/caffeine ($p \leq 0.001$). The proportions of patients with no photophobia or no phonophobia were superior after treatment with rizatriptan compared to ergotamine/caffeine from 1 h onwards. At 2 h, the proportions of patients with no photophobia were 71.4 vs. 50.0% ($p \leq 0.001$) and no phonophobia 78.7 vs. 55.7% ($p \leq 0.001$) for rizatriptan and ergotamine/caffeine, respectively. Fewer patients experienced vomiting with rizatriptan than with ergotamine/caffeine (3.8 vs. 10.5% at 2 h, $p \leq 0.001$).

*Functional Disability*

Rizatriptan was superior to ergotamine/caffeine in the proportion of patients with normal function from 1 h onwards. Almost 57% of patients on rizatriptan had normal function at 2 h versus 27.8% of patients taking ergotamine/caffeine ($p \leq 0.001$).

*Freedom from Pain and Associated Symptoms*

Two hours after treatment with rizatriptan, more patients had complete resolution of recorded migraine symptoms (namely no headache, no nausea, no vomiting, no photophobia, no phonophobia and no functional disability) than after treatment with ergotamine/caffeine (41.1 vs. 17.3%, $p \leq 0.001$).

*Satisfaction with Medication at 2 h*

Two hours after dosing, 69.8% of patients were satisfied (completely, very or somewhat) with rizatriptan, while 38.6% were satisfied with ergotamine/caffeine ($p \leq 0.001$). On the more stringent criteria of 'completely' or 'very satisfied', 43.8% of rizatriptan and 21.6% of ergotamine/caffeine patients reported this ($p \leq 0.001$).

*Sustained Pain Freedom and Sustained Headache Relief*

Sustained pain freedom, defined as being pain free at 2 h and with no recurrence or use of additional medication from 2 to 24 h, may be a useful combination of initial response and duration of clinical effect. Sustained pain freedom is superior to sustained headache relief (headache relief at 2 h, with no recurrence or use of additional medication from 2 to 24 h), pain freedom at 2 h and headache relief at 2 h over all domains of a validated 24-hour quality of life scale [12, 13]. More patients had sustained headache relief and sustained pain freedom with rizatriptan than with ergotamine/caffeine (47.6 vs. 34.0%, $p \leq 0.001$, and 35.6 vs. 20%, $p \leq 0.001$ respectively).

*Efficacy in Menstrually Associated Migraine*

In menstrually associated migraine attacks, the pain-free rates were 54.8% for rizatriptan and 15.4% for ergotamine/caffeine. In nonmenstrually associated migraine attacks, these rates were 49.7 and 26.4%, respectively. The treatment effect was consistent across the menstrually and nonmenstrually associated migraine attacks (p value interaction = 0.220).

*Need for Additional Medication from 2 to 24 h*

The percentages of patients taking additional medication from 2 to 24 h are shown in table 4. The most common medications taken were acetaminophen, ibuprofen and aspirin. Patients took less additional medication following rizatriptan than ergotamine/caffeine (27.7 vs. 45.5%, $p \leq 0.001$). The need for further treatment between 2 and 4 h after dose (the earliest period that patients could take additional medication) was also lower for patients receiving rizatriptan (14.5%) than for patients receiving ergotamine/caffeine (36.8%, $p \leq 0.001$).

*Headache Recurrence within 24 h*

Approximately 31.4% of patients on rizatriptan and 15.3% of patients taking ergotamine/caffeine reported recurrence and 28.7 and 13.8% treated the recurrence with a second dose of study medication, respectively. The mean time to recurrence from the time of first recorded pain relief was 14.7 and 12.5 h for the rizatriptan and ergotamine/caffeine groups, respectively. Interpretation of these figures is difficult because recurrence is both conditional on initial headache relief at 2 h and confounded by the use of additional medication.

*Tolerability*

Both treatments were generally well tolerated, and the AEs that did occur were mostly rated as mild or moderate in intensity and transient. Table 5 summarizes the clinical AE profile of the two agents. All 439 patients who treated at least one migraine attack with study medication were included in the safety analyses. 401 attacks were treated with rizatriptan 10 mg and 400 attacks were treated with ergotamine/caffeine. The overall incidence of any clinical AEs was similar between the rizatriptan and ergotamine/caffeine groups (35.4 vs. 34.5%). There were 2 serious AEs following rizatriptan. One patient had a headache of moderate intensity that led to hospitalization. This AE started at the same time of rizatriptan intake for the first treatment period and was considered definitely not drug

Table 5. Summary of overall incidence of clinical AEs and the most common clinical AEs (incidence ≥5% in any one treatment group)

| Patients | Rizatriptan 10 mg (n = 401) | | Ergotamine 2 mg + caffeine 200 mg (n = 400) | |
|---|---|---|---|---|
| | n | % | n | % |
| With one or more clinical AEs | 42 | 35.4 | 138 | 34.5 |
| With drug-related clinical AEs | 92 | 22.9 | 93 | 23.3 |
| With common clinical AEs | | | | |
| Dizziness | 27 | 6.7 | 21 | 5.3 |
| Somnolence | 22 | 5.5 | 9 | 2.3 |
| Nausea | 17 | 4.2 | 34 | 8.5 |
| Chest pain | 3 | 0.7 | 3 | 0.8 |

Although a patient may have had 2 or more AEs, the patient is counted only once within a category. The same patient may appear in different categories.

related by the investigator. One patient had a serious AE more than 14 days after treatment intake (pregnancy 72 days after treatment intake and spontaneous abortion 144 days after treatment intake, both definitely not related to study drug). The most common AEs (incidence ≥5% in one group) after rizatriptan and ergotamine/caffeine, respectively, were dizziness (6.7 and 5.3%), nausea (4.2 and 8.5%) and somnolence (5.5 and 2.3%). The incidence of chest pain was also low, reported by 0.7% of the patients following rizatriptan and 0.8% of patients after treatment with ergotamine/caffeine. There was no increase in the cardiovascular AE rate in patients with a family history of diabetes or cardiovascular disease, or in those who currently smoked, although the total number of events (n = 20) in the study was low.

## Discussion

The results of this double-blind active comparator study in 439 migraine patients indicate that rizatriptan 10 mg has important advantages over ergotamine/caffeine 2/200 mg in the treatment of migraine. On the coprimary outcome measure of preference, more than twice as many patients preferred rizatriptan to ergotamine/caffeine. It is important to note that the most important reason for preference was that rizatriptan relieved headache faster than ergotamine/caffeine. Likewise, those patients who preferred ergotamine/caffeine to rizatriptan did so for the same reason. The observation that speed of relief is most important to patients has been seen both in a previous open label preference study [14] comparing rizatriptan to sumatriptan and in surveys of migraine patients [15]. Preference is a readily understood concept that translates study data into clinical application and is clinically meaningful to patients. Preference was greater on the second attack and was independent of the agent taken to treat this attack. This observation may be due to recall bias.

Rizatriptan was also better than ergotamine/caffeine on a wide range of other outcome measures assessed within 2 h of dosing. It was superior concerning the percentage of patients who were pain free at 2 h (the International Headache Society standard for assessing efficacy in clinical trials in migraine) [16], as well as associated migraine symptoms (nausea, vomiting, photophobia and phonophobia) and those returning to normal function at 2 h. The higher pain rates with ergotamine than seen in a recent eletriptan comparison study [7] may be due either to the lack of a placebo group or a differing study population. At 2 h after dose, patients were more satisfied after rizatriptan than after ergotamine/caffeine. More patients had complete relief of acute migraine symptoms with rizatriptan than ergotamine/caffeine. In addition, rizatriptan provided a longer clinical effect, as defined by greater sustained headache relief and sustained pain-free rates. These results support the European Consensus guidelines on ergotamine which conclude, 'for most migraine sufferers requiring a specific anti-migraine treatment, a triptan is generally a better option ...' [17]. It is interesting to note that more patients treated with ergotamine reported nausea at 2 h, and in this study ergotamine also appears to induce nausea (post hoc analysis). Likewise, the lower recurrence rate seen with ergotamine than rizatriptan corroborates previous comparisons of dihydroergotamine with sumatriptan [18, 19].

Both active treatments were generally well tolerated. AEs were mostly mild or moderate and transient in nature. The commonest AEs following rizatriptan were similar to those reported in previous studies [1, 2, 14] and consisted of somnolence, dizziness and nausea.

In conclusion, rizatriptan 10 mg is preferred to ergotamine/caffeine. It is more effective in treating associated migraine symptoms and functional disability than ergotamine/caffeine, with headache relief and pain freedom occurring faster than with ergotamine/caffeine. Both rizatriptan and ergotamine/caffeine are well tolerated.


## Acknowledgements

S.C. has received financial support in the form of research grants and/or consulting fees and/or lecture honoraria from Merck Frost, GlaxoSmithKline, Astra Zeneca, Allergan and Biogen. H.G. received financial support in the form of research grants and/or consulting fees and/or lecture honoraria from MSD, Bayer, Janssen-Cilag, Lichtwer, Berlin-Chemie, Schwarz-Pharma, Almirall-Prodesfarma, Ipsen-Pharma, Fujisawa, Pfizer, Astra Zeneca, GlaxoSmithKline and Allergan. V.M. has received financial support in the form of research grants and/or consulting fees and/or lecture honoraria from MSD Spain, Almirall-Prodesfarma, Astra Zeneca and GlaxoSmith Kline. C.A., F.V. and M.S. are salaried employees of Merck & Co. Inc.


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