Oral Rizatriptan Versus Oral Sumatriptan: A Direct Comparative Study in the Acute Treatment of Migraine

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Rizatriptan is a potent, oral, 5-HT₁D agonist with more rapid absorption and higher bioavailability than oral sumatriptan. It was postulated that this would result in more rapid onset of effect. This randomized, double-blind, triple-dummy, parallel-groups study compared rizatriptan 5 mg, rizatriptan 10 mg, sumatriptan 100 mg, and placebo in 1268 outpatients treating a single migraine attack. Headache relief rates after rizatriptan 10 mg were consistently higher than sumatriptan at all time points up to 2 hours, with significance at 1 hour (37% versus 28%, P<0.01). All active agents were significantly superior to placebo with regard to headache relief and pain freedom at 2 hours (P<0.001). The primary efficacy endpoint of time to pain relief through 2 hours demonstrated that, after adjustment for age imbalance, rizatriptan 10 mg had earlier onset than sumatriptan 100 mg (P=0.032; hazard ratio 1.21). Rizatriptan 10 mg was also superior to sumatriptan in pain-free response (P=0.032), reduction in functional disability (P=0.015), and relief of nausea at 2 hours (P=0.010). Significantly fewer drug-related clinical adverse events were reported after rizatriptan 10 mg (33%, P=0.014) compared with sumatriptan 100 mg (41%). We conclude that rizatriptan 10 mg has a rapid onset of action and relieves headache and associated symptoms more effectively than sumatriptan 100 mg.

Key words: rizatriptan, sumatriptan, migraine

Abbreviations: AEs adverse events

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Migraine affects about 25% of women and 9% of men. Over half of all sufferers complain that their migraine attacks significantly restrict their work or social life. Patients have a strong preference for a drug which acts quickly in relieving the headache and migraine symptoms.

The newly-developed 5-HT₁D selective receptor agonist, rizatriptan, has three putative mechanisms of antimigraine action: (1) vasoconstriction of dilated meningeal blood vessels, (2) inhibition of the release of vasoactive neuropeptides from perivascular trigeminal sensory neurons, and (3) within the trigeminal nucleus caudalis, interruption of pain signals from the meninges.

As rizatriptan has more rapid absorption (T_max approximately 1 hour) and higher bioavailability (approximately 42%) than oral sumatriptan, the prototype 5-HT₁D agonist, we hypothesized that rizatriptan would have a faster onset of action and provide earlier relief of headache and other migraine symptoms. The primary objectives of this study were to compare rizatriptan 10 mg to sumatriptan 100 mg in terms of time to pain...
relief within 2 hours after dosing, and to compare the efficacy of both rizatriptan 5 mg and 10 mg with placebo at 2 hours. The 100-mg dose of sumatriptan was chosen as the comparator, because at study onset the recommended dose for sumatriptan was 100 mg throughout most of Europe, including the countries that participated in the trial. The safety and tolerability of rizatriptan 5 mg and 10 mg were also evaluated.

METHODS

Criteria for Patient Selection.—A total of 1268 men and women (18 to 65 years), who met IHS criteria for migraine with or without aura, were enrolled. All patients had at least a 6-month history of migraine, typically experienced one to eight attacks per month which could be distinguished from tension or interval headaches, and were in good health. Patients were excluded if there was clinical evidence of cardiovascular disease, hypertension, or significant electrocardiogram (ECG) abnormality, or if they had a known history (within 1 year) or current evidence of drug or alcohol abuse. Women who were pregnant or breast-feeding, patients with prior exposure to rizatriptan, those with any contraindication or sensitivity to sumatriptan, or those who had received treatment with any other investigational compound or device within the past 30 days were also excluded.

Approvals were obtained from the necessary regulatory bodies and ethical review committees, and informed consent was signed by each patient who participated in the trial. The study was conducted in accordance with the Declaration of Helsinki and conformed to Good Clinical Practice.

Study Design and Treatment Schedule.—This randomized, placebo-controlled, triple-dummy, double-blind, single-dose, outpatient study was conducted at 47 sites in 21 countries. All patients underwent a pre-study medical and migraine history, physical examination, laboratory tests, and a 12-lead ECG. In addition, patients completed a practice diary card to ensure full comprehension. Eligible patients were randomly assigned to treatment according to a double-blind computer-generated schedule. More patients were allocated to the rizatriptan 10-mg and sumatriptan 100-mg groups, because comparison between these groups was one of the primary objectives of this study. The other primary objective, to compare rizatriptan 5 and 10 mg to placebo, was satisfied by the smaller number of patients in the 5-mg group. Each dose of study medication consisted of three tablets (each distinct in appearance): either one active and two placebo tablets (to match the other two active treatments) or three placebo tablets.

Patients took the study medication for a migraine that was not resolving spontaneously and was of moderate or severe intensity (grade 2 or 3 on a 4-point headache severity scale), provided that they had not taken any prohibited medications (monoamine oxidase inhibitors, methysergide, and lithium within the past 2 weeks; sumatriptan, Midrin, or ergot derivatives within the past 48 hours; any opiate within 24 hours; any other form of analgesia or any antiemetic within the past 6 hours). Standard migraine prophylaxis was permitted, with the exception of non-steroidal anti-inflammatory drugs (NSAIDs). Non-responders were permitted optional escape analgesia and antiemetics at 2 hours postdose. Patients who, within 24 hours of taking the study medication, experienced recurrent headache (return to grade 2 or 3 after initial relief to grade 0 or 1 at 2 hours postdose), were allowed additional analgesia. Sumatriptan, Midrin, and ergot derivatives were prohibited for 24 hours postdose.

Clinical Efficacy and Safety Evaluation.—Primary and secondary measures were recorded by the patient in a diary. At baseline (0 hours) and at 0.5, 1, 1.5, 2, 3, and 4 hours after dosing, patients rated their headache severity, level of functional disability, and the presence or absence of associated symptoms (nausea, vomiting, photophobia, and phonophobia). Pain relief was defined as an improvement from severe or moderate headache (grade 3 or 2) to mild or no pain (grade 1 or 0), with pain-free being an improvement to no pain. At 2 hours postdose, patients recorded their need for escape medication. The time and maximum intensity of any headache recurrence were also recorded.

All postdose adverse events (AEs) were evaluated by the investigator at the posttreatment visit as to their maximum intensity, duration, seriousness, and relationship to test drug. In addition, the physical examination, laboratory tests, and electrocardiogram recordings were repeated.

Statistical Analyses and Power Calculations.—The primary comparisons were time to pain relief for rizatriptan 10 mg versus sumatriptan 100 mg within 2 hours, and pain relief at 2 hours for rizatriptan 5 mg and 10 mg ver-
sus placebo. Traditionally, migraine studies have analyzed an endpoint at 2 hours and de-emphasized other time points. However, endpoints occurring before 2 hours are also important to the patient, and the assessment of time-to-event as an endpoint (ie, survival analysis) is commonly used in medicine. The time-to-pain-relief analysis (a form of life table analysis) uses data from all gathered time points (0.5 to 2 hours) rather than just a single 2-hour time point to calculate a hazard ratio comparing treatments. The hazard ratio at time “t” is the ratio of probabilities to have pain relief in the very near future of time “t” if there was no relief at “t,” when comparing one treatment to another. This hazard ratio, considered constant in the 2-hour time interval, expresses whether a patient will respond more rapidly to one treatment compared to another and, therefore, whether one treatment is superior to another treatment with respect to time to pain relief. It has generally more power than a specific time point analysis without multiplicity issues and can also accommodate censoring (ie, patients with information up to a time point prior to 2 hours).

The primary efficacy analysis (intention-to-treat) included all patients who recorded at least one rating of pain severity after dosing (n=1096). Missing values were replaced by carrying forward the preceding value, except in the time-to-pain-relief analysis in which a patient was censored at the time there was no subsequent information. “Per protocol” analyses were also performed for the primary endpoints of time to pain relief (n=1042) and pain relief (n=1039). The primary efficacy measure was also investigated in a predefined fashion with regard to a number of potentially confounding factors (baseline headache severity, sex, age). The active treatment groups were compared with respect to time to pain relief by means of binary regression model with complementary log-log link for grouped time-to-event data. Pain relief, pain-free, and associated symptoms were analyzed by logistic regression, and functional disability was analyzed through cumulative logistic regression. All models included terms for treatment, region (groups of countries), and time (for the time-to-pain-relief analysis). Adverse experiences were compared using the Fisher exact test.

With a preplanned sample size of 375 patients in both the rizatriptan 10-mg and sumatriptan 100-mg groups, the study had 80% power to detect a 10 percentage point difference between these groups in percentages of responders at 1.5 hours postdose (based on a two-sided test type I error rate, α=0.05). The power to detect a hazard ratio of 1.32 in the time-to-pain-relief analysis was 76%. The power to detect a difference of 20 percentage points in relief at 2 hours in the rizatriptan 10 mg (n=375) and rizatriptan 5 mg (n=150) versus placebo (n=150) comparisons was greater than 95%. Adjustment for the rizatriptan 5 mg and 10 mg with placebo comparisons was made using the Hochberg procedure. The study was not powered to conduct a formal statistical analysis of headache recurrence rates. All 1099 patients who took study medication were included in the safety analysis.

RESULTS

Patient Characteristics.—A total of 1268 patients, 1030 women (81%) and 238 men (19%), were randomized to treatment. Of the 1099 who took the study drug, 1091 completed the study and 8 patients discontinued due to: clinical AE (n=1), lost to follow-up (n=2), withdrew from study (n=1), and deviated from protocol (n=4).

The baseline characteristics of the patients who took the study drug are displayed in Table 1. The treatment groups were generally similar, except that the patients in the rizatriptan 10-mg group were younger than the patients in the sumatriptan 100-mg group (37.0 versus 39.2 years, P=0.003).

Efficacy.—The percentages of patients reporting pain relief and pain-free response up to 2 hours are presented in Table 2. All active treatments were superior to placebo at 2 hours postdose (P<0.010). The hazard ratio for time to pain relief for rizatriptan 10 mg versus sumatriptan 100 mg was 1.17 (95% CI 0.98 to 1.39, P=0.075), suggesting that patients on rizatriptan 10 mg might be more likely to achieve pain relief at any time in the 2-hour period after treatment than patients on sumatriptan 100 mg. However, given that the sumatriptan group was significantly older, an age-adjusted analysis was conducted to correct this imbalance. This analysis revealed that rizatriptan 10 mg had a significantly faster time to pain relief than sumatriptan 100 mg (hazard ratio 1.21, P=0.032). Confirmation that rizatriptan 10 mg relieved migraine faster than sumatriptan 100 mg was also obtained in the prespecified (non-age-adjusted) “per protocol” analysis (P=0.040, hazard ratio 1.20 [95% CI 1.01 to 1.44]). Furthermore, riza-
Table 1.—Baseline Demographic Characteristics of Treated Patients (n=1099)

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=160)</th>
<th>Rizatriptan 5 mg (n=164)</th>
<th>Rizatriptan 10 mg (n=387)</th>
<th>Sumatriptan 100 mg (n=388)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, No. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>132 (82)</td>
<td>138 (84)</td>
<td>319 (82)</td>
<td>309 (80)</td>
</tr>
<tr>
<td>Male</td>
<td>28 (18)</td>
<td>26 (16)</td>
<td>68 (18)</td>
<td>79 (20)</td>
</tr>
<tr>
<td>Age, y</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>38.3 ± 10.3</td>
<td>38.3 ± 10.3</td>
<td>37.0 ± 10.0</td>
<td>39.2 ± 10.1*</td>
</tr>
<tr>
<td>Median (range)</td>
<td>38.0 (18-65)</td>
<td>37.0 (19-65)</td>
<td>37.0 (18-62)</td>
<td>39.0 (18-65)</td>
</tr>
<tr>
<td>Baseline headache</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>characteristics, No. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>84 (53)</td>
<td>92 (56)</td>
<td>213 (55)</td>
<td>196 (51)</td>
</tr>
<tr>
<td>Moderate</td>
<td>75 (47)</td>
<td>72 (44)</td>
<td>174 (45)</td>
<td>191 (49)</td>
</tr>
<tr>
<td>Migraine with aura</td>
<td>26 (16)</td>
<td>22 (13)</td>
<td>69 (18)</td>
<td>69 (18)</td>
</tr>
<tr>
<td>Baseline functional</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>disability, No. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal function</td>
<td>4 (2)</td>
<td>4 (2)</td>
<td>22 (6)</td>
<td>10 (3)</td>
</tr>
<tr>
<td>Mildly impaired</td>
<td>60 (38)</td>
<td>51 (31)</td>
<td>132 (34)</td>
<td>140 (36)</td>
</tr>
<tr>
<td>Severely impaired</td>
<td>62 (39)</td>
<td>74 (45)</td>
<td>144 (37)</td>
<td>160 (41)</td>
</tr>
<tr>
<td>Required bed rest</td>
<td>33 (21)</td>
<td>35 (21)</td>
<td>89 (23)</td>
<td>77 (20)</td>
</tr>
</tbody>
</table>

* P<0.01 versus rizatriptan 10 mg.
† Two patients had not recorded baseline severity (one on placebo and one on sumatriptan 100 mg).

Table 2.—No. (%) of Patients Reporting Pain Relief and Pain-Free up to 2 Hours

<table>
<thead>
<tr>
<th>Hours</th>
<th>Placebo (n=159)</th>
<th>Rizatriptan 5 mg (n=164)</th>
<th>Rizatriptan 10 mg (n=385)</th>
<th>Sumatriptan 100 mg (n=387)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pain relief</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.5</td>
<td>19 (12)</td>
<td>19 (12)</td>
<td>50 (13)</td>
<td>43 (11)</td>
</tr>
<tr>
<td>1</td>
<td>32 (20)</td>
<td>49 (30)</td>
<td>141 (37)*†</td>
<td>108 (28)</td>
</tr>
<tr>
<td>1.5</td>
<td>57 (36)</td>
<td>73 (45)</td>
<td>206 (54)*†</td>
<td>182 (47)*†</td>
</tr>
<tr>
<td>2</td>
<td>64 (40)</td>
<td>99 (60)*</td>
<td>258 (67)*</td>
<td>239 (62)*</td>
</tr>
<tr>
<td></td>
<td>Pain-free</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.5</td>
<td>3 (2)</td>
<td>1 (1)</td>
<td>6 (2)</td>
<td>5 (1)</td>
</tr>
<tr>
<td>1</td>
<td>5 (3)</td>
<td>11 (7)</td>
<td>40 (10)§</td>
<td>30 (8)</td>
</tr>
<tr>
<td>1.5</td>
<td>12 (8)</td>
<td>27 (17)§</td>
<td>91 (24)**†</td>
<td>68 (18)§</td>
</tr>
<tr>
<td>2</td>
<td>15 (9)</td>
<td>41 (25)*</td>
<td>155 (40)**†</td>
<td>127 (33)*</td>
</tr>
</tbody>
</table>

* P<0.001 versus placebo.
† P<0.05 versus sumatriptan.
‡ P<0.005 versus placebo.
§ P<0.01 versus placebo.
|| P<0.01 versus rizatriptan 5 mg.
### Table 3—Secondary Efficacy Measures

<table>
<thead>
<tr>
<th>Outcome Measure</th>
<th>Placebo</th>
<th>Rizatriptan 5 mg</th>
<th>Rizatriptan 10 mg</th>
<th>Sumatriptan 100 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Functioning normally*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 h</td>
<td>4/159 (3)</td>
<td>4/164 (2)</td>
<td>22/387 (6)</td>
<td>10/387 (3)</td>
</tr>
<tr>
<td>2 h</td>
<td>31/159 (20)</td>
<td>52/164 (32)†</td>
<td>160/385 (42)‡§‖</td>
<td>126/387 (33)†</td>
</tr>
<tr>
<td>Without nausea</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 h</td>
<td>61/159 (38)</td>
<td>71/163 (44)</td>
<td>158/387 (41)</td>
<td>153/385 (40)</td>
</tr>
<tr>
<td>2 h</td>
<td>91/159 (57)</td>
<td>127/164 (77)‡§‖</td>
<td>290/385 (75)‡§‖</td>
<td>259/387 (67)§</td>
</tr>
<tr>
<td>Without photophobia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 h</td>
<td>46/159 (29)</td>
<td>38/164 (23)</td>
<td>96/387 (25)</td>
<td>92/385 (24)</td>
</tr>
<tr>
<td>2 h</td>
<td>75/159 (47)</td>
<td>94/164 (57)</td>
<td>238/385 (61)†</td>
<td>225/387 (58)§</td>
</tr>
<tr>
<td>Without phonophobia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 h</td>
<td>48/159 (30)</td>
<td>45/163 (28)</td>
<td>99/387 (26)</td>
<td>108/385 (28)</td>
</tr>
<tr>
<td>2 h</td>
<td>76/159 (48)</td>
<td>103/164 (63)†</td>
<td>254/385 (66)†</td>
<td>234/387 (60)†</td>
</tr>
</tbody>
</table>

* Treatment comparisons were based on all four categories of functional disability.
† P<0.01 versus placebo.
‡ P<0.001 versus placebo.
§ P<0.05 versus sumatriptan.
‖ P<0.05 versus rizatriptan 5 mg.
†† P<0.05 versus placebo.

Rizatriptan 10 mg showed a numerically greater response rate over sumatriptan 100 mg at each time point up to 2 hours, reaching statistical significance at 1 hour (37% versus 28%, P=0.010). By 4 hours, the response rates (84%) in the rizatriptan 10-mg and sumatriptan 100-mg groups (P=0.787) were similar, and both were superior to rizatriptan 5 mg (P=0.002 and P=0.004, respectively). However, the 4-hour response rates may be confounded by the use of escape medications which were permitted after 2 hours postdose.

In terms of the percentage of patients reporting freedom from pain, rizatriptan 10 mg was significantly superior to placebo starting at 1 hour, while rizatriptan 5 mg and sumatriptan 100 mg did not significantly differentiate from placebo until 1.5 hours. Importantly, rizatriptan 10 mg rendered significantly more patients pain-free at 1.5 hours (P=0.038) and 2 hours (P=0.032) postdose when compared with sumatriptan 100 mg.

Functional disability was significantly improved in all active treatment groups at 2 hours (Table 3). More patients receiving rizatriptan 10 mg as compared with sumatriptan 100 mg reported normal function at 1 hour (14% versus 9%, P=0.031), 1.5 hours (27% versus 19%, P=0.017), and 2 hours (42% versus 33%, P=0.015), indicating an advantage for rizatriptan 10 mg on this parameter, whereas the percentage of patients with functional disability up to 2 hours postdose were similar in the rizatriptan 5-mg and sumatriptan 100-mg groups.

Significantly more patients were free of nausea at 2 hours postdose in all active groups compared with placebo. When compared with sumatriptan 100 mg, significantly more patients in the rizatriptan 10-mg group were without nausea at all time points through 2 hours (P<0.01); this advantage over sumatriptan 100 mg was also observed in
Table 4.—Adverse Events Reported in >5% of Patients

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Placebo (n=160)</th>
<th>Rizatriptan 5 mg (n=164)</th>
<th>Rizatriptan 10 mg (n=387)</th>
<th>Sumatriptan 100 mg (n=388)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Somnolence</td>
<td>9 (6)</td>
<td>12 (7)</td>
<td>33 (9)</td>
<td>28 (7)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>6 (4)</td>
<td>9 (6)</td>
<td>30 (8)</td>
<td>35 (9)</td>
</tr>
<tr>
<td>Asthenia/fatigue</td>
<td>6 (4)</td>
<td>4 (2)*†</td>
<td>30 (8)</td>
<td>32 (8)</td>
</tr>
<tr>
<td>Nausea</td>
<td>4 (3)</td>
<td>8 (5)</td>
<td>22 (6)</td>
<td>35 (9)‡</td>
</tr>
<tr>
<td>Vomiting</td>
<td>8 (5)</td>
<td>5 (3)</td>
<td>12 (3)</td>
<td>10 (3)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>2 (1)</td>
<td>7 (4)</td>
<td>12 (3)</td>
<td>20 (5)</td>
</tr>
<tr>
<td>Chest pain</td>
<td>4 (3)</td>
<td>2 (1)†</td>
<td>13 (3)</td>
<td>22 (6)</td>
</tr>
<tr>
<td>Any adverse event</td>
<td>51 (32)</td>
<td>64 (39)§</td>
<td>180 (47)‡</td>
<td>202 (52)</td>
</tr>
<tr>
<td>Any drug-related adverse event</td>
<td>32 (20)</td>
<td>45 (27)§</td>
<td>126 (33)†</td>
<td>161 (41)†</td>
</tr>
</tbody>
</table>

Values given in No. (%) of patients.

* P<0.05 versus rizatriptan 10 mg.
† P<0.05 versus sumatriptan 100 mg.
‡ P<0.01 versus placebo.
§ P<0.01 versus sumatriptan 100 mg.
|| P<0.001 versus placebo.

the rizatriptan 5-mg group at 1 through 2 hours (P≤0.01). All active treatments were superior to placebo at 2 hours postdose in relieving phonophobia and photophobia. A post hoc analysis in only those patients who had nausea, photophobia, or phonophobia at baseline showed that rizatriptan 10 mg relieved these associated symptoms significantly better through 2 hours posttreatment than sumatriptan 100 mg (nausea: odds ratio 0.63, 95% CI 0.46 to 0.86, P<0.05; photophobia: OR 0.67, CI 0.48 to 0.93, P<0.05; phonophobia: OR 0.69, CI 0.50 to 0.94, P<0.05).

Fewer patients required escape medication after 2 hours in the rizatriptan 10-mg (18%, P<0.001) and sumatriptan 100-mg (20%, P=0.003) groups compared with patients in the placebo group (32%). The headache recurrence rates were similar for the rizatriptan 10-mg (35%) and sumatriptan 100-mg (32%) groups, and somewhat higher in the rizatriptan 5-mg (48%) group, compared to a rate of 20% in the placebo group.

Safety.—Most AEs were mild or moderate in intensity. Both rizatriptan 10 mg and sumatriptan 100 mg were associated with more drug-related AEs in comparison to placebo (126 [33%] of 387 patients in the rizatriptan 10-mg group and 160 [41%] of 388 patients in the sumatriptan 100-mg group versus 32 [20%] of 160 patients in the placebo group, P values <0.01). The incidence in the rizatriptan 10-mg group was lower than that in the sumatriptan 100-mg group (P=0.014). Rizatriptan 5 mg was similar to placebo in the percentage of drug-related AEs (45 [27%] of 164 patients, P=0.120), and the incidence did not differ significantly from that for rizatriptan 10 mg (P=0.268). Rizatriptan 5 mg was also associated with significantly fewer drug-related AEs than sumatriptan 100 mg (P=0.002). The most prevalent AEs, regardless of causality, are presented in Table 4. Of these, only three significant differences were detected: (1) compared with rizatriptan 5 mg, more patients in the rizatriptan 10-mg (P=0.019) and sumatriptan 100-mg (P=0.013) groups reported asthenia/fatigue; (2) after rizatriptan 5 mg, fewer patients reported chest pain than after sumatriptan 100 mg (P=0.02); and (3) of the active treatments, only sumatriptan 100 mg produced more reports of nausea than placebo (P=0.006). One patient, a woman in the sumatriptan 100-mg group, discontinued due to a drug-related clinical AE (transient emesis). There were no serious drug-related AEs reported during the study. No trends for changes in laboratory parameters, blood pressure, heart rate, or electrocardiogram recordings were noted.

COMMENTS

This large multinational study demonstrated signifi-
cant and clinically relevant differences between therapeu-
tic oral doses of the 5-HT\textsubscript{1B/1D} agonists, rizatriptan and
sumatriptan, which may be related to faster absorption of
rizatriptan.\textsuperscript{10} While both agents were highly effective and
well-tolerated, rizatriptan 10 mg demonstrated greater
effectiveness over a range of other outcome measures.
Additionally, after correction for age and by per protocol
analysis, rizatriptan 10 mg showed faster pain relief than
sumatriptan 100 mg. Furthermore, patients taking rizatrip-
tan 10 mg were more likely to be completely relieved of
head pain (pain-free response) at 1.5 and 2 hours compared with sumatriptan 100 mg.

The therapeutic advantage of rizatriptan 10 mg versus
sumatriptan 100 mg was also reflected in a better reduc-
tion of functional disability, and in faster and more effec-
tive relief of nausea. Finally, it is noteworthy that the
increased efficacy of rizatriptan 10 mg does not appear to
be accompanied by an increase in overall side effects rela-
tive to sumatriptan 100 mg. In conclusion, this study
showed that rizatriptan 10 mg had a fast onset of action
and relieved migraine more effectively than sumatriptan
100 mg, with both compounds having an acceptable safe-
ty and tolerability profile.

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A. Ming, M. Aguilar, I. Corral, and M. De Bestos.

REFERENCES
1. Headache Classification Committee of the
International Headache Society. Classification and
diagnostic criteria for headache disorders, cranial
neuralgias and facial pain. Cephalalgia. 1998;8(suppl
7):1-96.
2. Rasmussen BK, Jensen R, Schroll M, Olesen J.
Epidemiology of headache in a general population—a
prevalence study. J Clin Epidemiol. 1991;44:1147-
1157.
Murray TJ, Nelson RF. A Canadian population survey
on the clinical, epidemiologic and societal impact of
migraine and tension-type headache. Can J Neurol
4. Gobel H, Petersen-Braun M, Heinze A. Which prop-
erties do patients expect of new and improved drugs
in the treatment of primary headache disorders? In:
Olesen J, Tfelt-Hansen P, eds. Headache Treatment:
Trial Methodology and New Drugs. New York:
pharmacological profile of rizatriptan. Cephalalgia.
Rizatriptan selectively contracts human middle
meningeal over coronary artery: comparison
Abstract.
7. Williamson DJ, Shepheard SL, Hill RG, Hargreaves
RJ. The novel anti-migraine agent rizatriptan inhibits
neurogenic dural vasodilation and extravasation. Eur
J Pharmacol. 1997;328:61-64.
8. Cumberbatch MJ, Hill RG, Hargreaves RJ.
Rizatriptan has central antinociceptive effects against
CR, Ferrari MD. Rizatriptan versus sumatriptan in
the acute treatment of migraine. A placebo-controlled,
human experience with MK-462 (rizatriptan): a novel
11. Fowler PA, Lacey LF, Thomas M, Keene ON, Tanner
RJ, Baber NS. The clinical pharmacology, pharmaco-
kinetics and metabolism of sumatriptan. Eur Neurol.
of its pharmacology and therapeutic efficacy in the
acute treatment of migraine and cluster headache.

