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Original Contributions

RIZATRIPTAN RPD FOR SEVERE MIGRAINE IN THE EMERGENCY DEPARTMENT—A MULTICENTER STUDY

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□ **Abstract—Many patients with severe migraine come to the Emergency Department (ED) due to failure of different drug regimens to stop their headache. We treated 98 patients with severe migraine who were seen in three different EDs. We used rizatriptan RPD wafers 10 mg and observed the patients for 2 h. We found that at 2 h, 92.9% (91/98) of the patients had pain relief, and 73.5% were pain free. The mean time to pain relief was 26.9 ± 29.6 min with a median of 15 min, and the time to pain free was 70.2 ± 47.3 min with a median of 75 min. Eighty-five percent of the patients were free of associated symptoms, such as nausea and vomiting, at 2 h with a mean time to symptom free of 55 ± 47.5 min and a median of 45 min. Rizatriptan was reported to be much better than other drugs by 74.4% of the patients. Side effects were minor and transient. Recurrence of migraine occurred part of the day in 17.1% of the patients and all day or almost all day in 8.6% of the patients only. The results were consistent in all three EDs. We conclude that rizatriptan RPD is very effective and reliable as a first-line therapy for acute migraine in the ED. It dissolves immediately in the mouth without the inconvenience of an injection. It works fast and has few side effects and low headache recurrence. © 2003 Elsevier Inc.**

□ **Keywords—migraine; rizatriptan; rizatriptan in ED; migraine in ED**

INTRODUCTION

Migraine affects 13 to 18% of women and 3 to 6% of men, with peak prevalence between 35 and 45 years of age (1,2). Although there is considerable variation in the severity and frequency of migraine attacks among patients and within individuals, more than half of all patients with migraines have restricted their work and their social life significantly (3). The exact pathophysiology of migraine remains poorly understood, but numerous studies support the neurovascular theory and the role of the serotonin 5-$HT_{1B/1D}$ receptor in relieving migraine headache (4–7).

Until the last decade, migraine patients had a rather limited choice of antimigraine drugs. Traditional therapies included simple analgesics such as acetaminophen and salicylates, nonsteroidal anti-inflammatory drugs, ergotamine, and antiemetic drugs (8). The revolution in migraine therapy began with the discovery of the triptan drugs, which activate the serotonin receptor 5-$HT_{1B/1D}$ and relieve the headache (6,9–11). Several triptan drugs are being marketed, including sumatriptan, naratriptan, zolmitriptan, and rizatriptan (Rizalt®). Other new triptans are under investigations. These drugs differ in their bioavailability, onset of action, duration of action,

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adverse reactions, their capability to penetrate the blood brain barrier (BBB), and activation of 5-HT receptors (11–13). Rizatriptan is a 5-$HT_{1B/1D}$ receptor agonist, which easily penetrates the BBB, is rapidly absorbed, and has a rapid onset of action (14–16). Studies with rizatriptan in two different doses, 5 and 10 mg, and in two forms, conventional tablets and rapidly dissolving freeze-dried (RPD) wafers 10 mg, showed that it is effective and well tolerated with low side effects and better quality of life after treatment (14,17–20). The RPD wafer dissolves immediately in the mouth and thus has the advantage of eliminating the need for drinking water. This form is best tolerated by the vomiting patient (20).

Patients with severe migraine attack often seek help in the Emergency Department (ED). Drugs usually used to treat acute migraine in the ED include parenteral opioids and phenothiazines (21–24). These drugs, although effective, are nonspecific and have many side effects, including severe hypotension (21–25). Sumatriptan subcutaneous injections have been used to treat acute migraine in the ED with good results, with the inconvenience of administering an injection. Hay reported a pain relief rate of 80% within 20 to 30 min, and pain free rate of 75% within 90 min (26). Akpunonu et al. reported a pain relief rate of 75% within 34 min, and 70% of the patients had mild or no pain at discharge (27).

Theoretically, rizatriptan RPD 10 mg wafers (RzRPD) would be superior due to its ease of administration, its rapid onset of action, and its specific antimigraine effect. For this reason, we conducted the following prospective unblinded study to examine the efficacy, tolerability, and quality of life after Rizatriptan RPD wafer (RzRPD) administration as a first-line therapy for acute migraine in the ED. The study was conducted simultaneously in three different Emergency Departments. The Institutional Board for Research in Human Beings did not approve the use of placebo for double-blind study. The members of the Board thought it was not ethical to give placebo to patients with severe headache in the ED. We could not obtain the agreement of other companies to conduct a double-drug double-blind study.

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MATERIALS AND METHODS

Patients over 18 years of age with known migraine [the International Headache Society (IHS) definition of migraine (28)] who came to the ED for acute migraine attack were considered eligible for the study. Patients were asked to grade their headache as mild, moderate, or severe to the degree that they refrained from any physical or social activity. Only patients who had at least one migraine attack per month during the last 6 months and graded their headache as severe were enrolled in the study. For all the patients, it was the first time that they ever took rizatriptan in any form for their migraine, but not necessarily their first experience with other triptans. Exclusion criteria are described in Table 1. Eligible patients were treated with RzRPD 10 mg wafer and observed for 2 h. Nonresponders, patients who had no improvement of their headache, and partial responders, patients who had pain relief but were not pain free, received other analgesics. During the 2-h observation period, we evaluated the following parameters every 15 min: time to cessation of associated symptoms; nausea and vomiting; photophobia and phonophobia; time to pain relief; time to pain free; and adverse reactions. Patients were discharged home or admitted to the hospital if their headache remained as severe as before.

Table 1. Exclusion Criteria

First attack of headache.
Age less than 18 or over 65 years.
Uncontrolled hypertension.
Unstable angina pectoris.
Basilar migraine.
Patients with severe renal failure.
Use of other triptans less than 24 h before beginning the study.
Known hypersensitivity to triptans.
Pregnancy and lactation.
Patients taking ergot derivatives, propranolol, SSRI and MAO inhibitors.

Two nurses conducted telephone interviews with each patient 24 h after discharge from the ED. Patients were asked to answer a quality-of-life questionnaire to evaluate the rate of migraine recurrence and associated symptoms, and any disability that interfered with the quality of life after discharge (29,30). Interference with quality of life was evaluated by the persistence of nervousness, restriction of social and work activities, disturbed concentration, sleep disturbance, and disturbed mood.

This study was approved by the Institutional Board for Research in Human Beings.

RESULTS

A total of 98 patients were enrolled in the study, 87.8% of them were women. The mean age was 40.39 ± 9.95, range 18–63 years. Table 2 summarizes the presence of associated symptoms among the patients, before and after RzRPD treatment. At 2 h, 90.6% of the patients were free of nausea, 100% stopped vomiting, 89% were free of phonophobia, and 90% were free of photophobia.

Table 2. Associated Symptoms Among Patients (N = 98)

Associated Symptom	Number of Patients Before RzRPD	Number of Patients 2 Hours After RzRPD
Nausea	64 (65.3%)	6 (9.4%)
Vomiting	24 (24.5%)	0 (0%)
Phonophobia	56 (57.1%)	6 (10.7%)
Photophobia	61 (62.2%)	6 (9.8%)

Ninety-one patients out of 98 (92.9%) had pain relief within 2 h and 73.5% of the patients were pain free by 2 h. The mean time to pain relief was 26.9 ± 29.6 min with a median of 15 min, and the mean time to pain free was 70.2 ± 47.3 min with a median of 75 min (Table 3). Eighty-five percent (85%) of the patients were free of associated symptoms within 2 h, with a mean time to symptom free of 55 ± 47.5 min and a median of 45 min. Rizatriptan was reported to be much better than other drugs ever used by 74.4% of the patients, 18.9% reported it as slightly better, and only 6.7% of the patients reported that it was similar to other drugs. None reported that it was worse than other therapies. The results of the three EDs were not significantly different, emphasizing the consistency of the effect of RzRPD.

Only a few patients reported side effects during the 2-h treatment schedule. The side effects are presented in Table 4. Side effects included: weakness in 4 patients and dizziness in 5 patients. Two patients experienced euphoria. All these side effects were transient and not necessarily related to rizatriptan RPD. Three patients were hospitalized for 24 h for continuous pain and their course was uneventful. Two of them were diagnosed with tension headache and the third with upper respiratory infection.

The results of the quality of life survey 24 h after discharge from the ED are presented in Table 5. Most of the patients (74.3%) had hardly any headache, 17.1% had headache part of the day, and 8.6% continued to experience headache all day or almost all day. More than half of the patients had restriction of normal activities and mood disturbances. About 40% of the patients had difficulties in concentration and interference with sleep.

Table 3. Time to Pain Relief, Symptom Free and Pain Free

	Mean (minutes)	Median (minutes)	% of patients
Time to pain relief	26.9 ± 29.6	15	92.9%
Time to symptom free	55 ± 47.5	45	85%
Time to pain free	70.2 ± 47.3	75	73.5%

Table 4. Side Effects During the 2-Hour Observation Period

	Number of patients
Weakness	4 (4.1%)
Diarrhea	1 (1%)
Euphoria	2 (2%)
Dizziness	5 (5.1%)
Shortness of Breath	1 (1%)
Fever	1 (1%)
Difficulty in concentration	1 (1%)

DISCUSSION

Our study demonstrates better efficacy of rizatriptan in achieving pain relief and pain free end points at 2 h than in previous studies. The majority of our patients, 92.9%, had pain relief with a median time to relief of 15 min vs. 67–80% found in other studies, and 73.5% were pain free by 2 h with a median of 75 min vs. 40–49% of the patients in different studies (16,17,19,20,31,32). The same is true for the percentage of symptom-free patients at 2 h: 85% in our study with a median time of 45 min vs. 22–75% in the same studies cited (Figure 1). We believe that these significant differences originate from the different design of the studies. Our patients were examined in the EDs, and it was the emergency physician who decided whether that headache was consistent with the definition of the IHS of migraine. It should be remembered that a migraine patient may also have a tension headache severe enough to be confused with acute migraine, and this patient will not respond properly to rizatriptan, meaning failure of treatment. Only those selected patients with acute migraine were treated with rizatriptan. One may conclude that the more specific the diagnosis of the attack, the better the response will be. Our results are also better than those achieved with

Table 5. Quality of Life 24 Hours After Release From the ED

	All day or almost all day	Part of the day	Hardly or none
Photophobia	8.2%	18.8%	73%
Phonophobia	14%	18.6%	67.4%
Nausea	8.3%	17.9%	73.3%
Recurrence of migraine	8.6%	17.1%	74.3%
Nervousness	9.5%	14.3%	76.2%
Restriction of normal life activities	23%	28.7%	48.3%
Disturbed concentration	23.8%	22.6%	53.6%
Interference with sleep	28.3%	9.4%	62.3%
Disturbed mood	26.5%	24.1%	49.4%

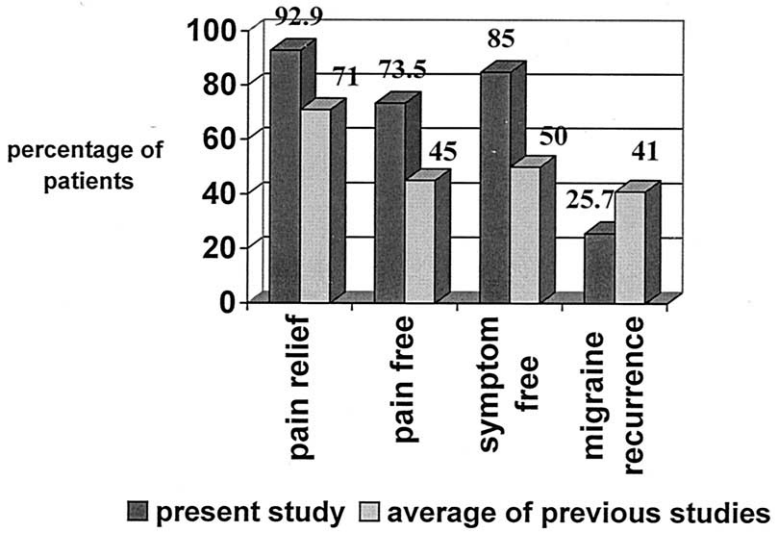

Figure 1. Present study results compared to average results of previous studies.

sumatriptan injection, and without the inconvenience of injection (26,27).

Regarding recurrence of migraine among rizatriptan 10 mg responders, it is reported to range between 35% and 47% (17–20,31). In our study, the rate of recurrence was much lower: 74.3% of the patients reported they had hardly any headache during the 24 h after discharge; 17.1% of the patients experienced headache part of the day and only 8.6% reported headache for the whole day. Again, these differences in the results might originate from the rigid selection of patients and from the different method of follow-up. In our study, two nurses conducted the telephone interviews and contacted every patient who was enrolled in the study. The nurses explained all the questions to the patients and the questionnaires were complete.

Rizatriptan also showed good results in the rest of the parameters of quality of life except for restriction of normal life activities, disturbed concentration, and disturbed mood. About half of the patients reported these disturbances all day or part of the day.

Despite these encouraging results, one should be aware of the limitations of the study. Partial responders took other analgesics that might affect the results, and patients were not offered a second tablet of rizatriptan, which could have changed the results. The same reservations were reported in other studies (17,18).

Comparing side effects that the patients reported, it is interesting that only few patients complained of adverse reactions, and many of the known side effects were not reported, such as chest pain, dry mouth, and abdominal pain. We don't have any explanation for that, but perhaps the migraine attack was so severe in our selected group that the patients ignored the side effects, or perhaps they thought that side effects were part of the migraine. Interestingly, two patients reported euphoria, a side effect that we did not find in other studies. A possible explanation is the activation of serotonin receptors by this serotonin agonist.

CONCLUSIONS

We find rizatriptan RPD wafer 10 mg to be very effective as a first-line therapy for acute migraine attack diagnosed by physicians in the ED. Most patients left the ED without pain and without the need for additional analgesics. The immediate side effects were minimal and most of the patients found it to be much better than any other drug. We strongly recommend the use of rizatriptan RPD 10 mg wafers for the treatment of acute migraine in the ED.

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