

Research Submission

Efficacy and Tolerability of Coadministration of Rizatriptan and Acetaminophen vs Rizatriptan or Acetaminophen Alone for Acute Migraine Treatment

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Objective.—To evaluate the efficacy and tolerability of coadministration of rizatriptan and acetaminophen in the acute treatment of migraine.

Background.—Rizatriptan is a selective 5-HT_{1B/1D} agonist approved for the acute treatment of migraine. Acetaminophen has been studied for acute migraine treatment. In consideration of the prominent central and peripheral mechanisms in migraine, the use of “multi-mechanism therapy” is gaining momentum in the treatment of acute migraine attacks.

Study Design.—This was a randomized, double-blind, placebo-controlled trial conducted at 10 centers. Eligible patients with migraine according to International Headache Society criteria treated a single migraine attack of moderate or severe intensity within 4 h from pain onset. Patients were randomized into 1 of 4 groups (rizatriptan 10 mg + acetaminophen 1000 mg [RA], rizatriptan alone [R], acetaminophen alone [A], and placebo [P]). There were 3 co-primary hypotheses tested sequentially for 2-h pain relief: (1) RA would be superior to P; (2) if the first was fulfilled, RA would be superior to A; and (3) if the first 2 were fulfilled, RA would be superior to R.

Results.—Of 173 patients who treated a migraine, 123 patients (71.5%) achieved pain relief within 2 h. RA (90%) was significantly better than P (46%) and A (70%), but only numerically better than R (77%) for 2-h pain relief. No significant differences were seen between the active treatment groups in adverse events.

Conclusion.—Rizatriptan coadministered with acetaminophen achieved 2 of the 3 primary hypotheses, proving superior to both acetaminophen and placebo for 2-h pain relief, but failing to achieve superiority to rizatriptan alone. RA was as well tolerated as each of the individual agents.

Key words: triptans, rizatriptan, acetaminophen, multi-mechanism therapy, monotherapy, acute migraine treatment

Abbreviations: IHS International Headache Society, mITT modified intention-to-treat, NSAID nonsteroidal anti-inflammatory drug

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INTRODUCTION

The concept of “multi-mechanism” therapy in acute migraine treatment is a response to recognition

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of central and peripheral mechanisms in migraine.¹ Several studies have indicated that, during a migraine attack, different pathways are activated.¹⁻³ Interrelated events are implicated in producing the symptom complex of migraine including pain, nausea, photophobia, phonophobia, and other autonomic symptoms. Researchers have attributed these symptoms to changes in both the central and peripheral nervous systems, with specific activation of the trigeminal nerve. These findings indicate the potential for effective therapy via multiple central and peripheral sites.

For the acute treatment of migraine, the current standards are either migraine-specific (ergots, triptans) or nonspecific (analgesics, opioids, barbiturates).⁴ The triptans are considered first-line agents in the abortive treatment of migraine for those with disabling migraine. However, for patients whose headaches are not typically disabling, the use of over-the-counter agents such as acetaminophen may prove sufficient for the treatment of migraine. The use of a centrally acting agent combined with a peripherally acting drug may produce more robust results than either agent alone. In recent studies, for example, combination therapy of sumatriptan and naproxen demonstrated increased efficacy vs the use of the component agents for acute migraine therapy.^{5,6}

Rizatriptan benzoate (Maxalt[®]; R) is a selective 5-HT_{1B/1D} agonist that is approved for the acute treatment of migraine.⁷ Acetaminophen (A) is commonly used for the treatment of pain and has been studied as an acute treatment for migraine.^{8,9} At the dose of 1000 mg, acetaminophen was demonstrated to be an effective monotherapy for the treatment of the pain, disability, and associated symptoms of phonophobia and photophobia in patients with migraine whose attacks were not typically disabling.⁹

At present, only a few studies have looked at the coadministration of rizatriptan with another agent for the acute treatment of moderate/severe migraine. An open-label pilot study examined the combination of rizatriptan and rofecoxib, a COX-2 enzyme inhibitor, vs rizatriptan alone and found that although pain freedom at 2 h was only numerically better for rizatriptan + rofecoxib than for rizatriptan alone, recurrence rates were lower for the combination.¹⁰ A second open-label study looked at rizatriptan alone,

rizatriptan + rofecoxib, and rizatriptan + tolenamic acid, a traditional nonsteroidal anti-inflammatory drug (NSAID), and showed that 2-h pain-free rates were significantly better for the rizatriptan + rofecoxib group vs both rizatriptan + tolenamic acid and rizatriptan alone.¹¹ A third study examined a combination of rizatriptan with trimebutine, a gastric motility agent, and demonstrated an improved response for the acute treatment of migraine when the 2 agents were used together compared with rizatriptan alone.¹² The current study was undertaken to evaluate the efficacy and tolerability of coadministration of rizatriptan and acetaminophen in the acute treatment of migraine. The combination was compared with rizatriptan alone, acetaminophen alone, and placebo.

METHODS

Patients.—The study enrolled patients with at least a 6-month history of migraine with or without aura as defined according to the International Headache Society (IHS) criteria.¹³ Patients included men and women (not pregnant or nursing), at least 18 years of age, who had the ability to distinguish between migraine attacks and other types of headache. Patients were excluded from participation in the study if they had more than 6 migraine attacks per month or typically had greater than 10 headache days per month or if they had a history of hemiplegic or basilar migraine. Those who had daily or almost daily (typically >3 days of 7 days) use of NSAIDs, COX-2 inhibitors, or other analgesics; monoamine oxidase inhibitors; or propranolol were excluded. Patients also were excluded if they had a history or clinical evidence of ischemic heart disease, coronary artery vasospasm (including Prinzmetal's variant angina), or other significant underlying cardiovascular disease or uncontrolled hypertension or clinical evidence of significant pulmonary, renal, hepatic, endocrine, neurologic (other than migraine), psychiatric, or any other condition that would pose an additional risk or interfere with optimal participation in the study, or if they had demonstrated hypersensitivity to or experienced a serious adverse event in response to rizatriptan, acetaminophen, or any of their inactive components.

Study Design.—This was a double-blind, double-dummy, randomized, parallel-group, placebo-

controlled study conducted at 10 centers in the United States between March and October of 2006. A total of 204 patients were enrolled in the study. The protocol was approved by both a central (Western Institutional Review Board, Olympia, WA) as well as several individual local institutional review boards and in keeping with the Declaration of Helsinki. All patients gave written informed consent to participate in the study before any study-related procedures were performed. Eligible subjects were randomly assigned according to a computer-generated allocation schedule to 1 of 4 treatment groups (1:1:1:1 ratio) using oral tablet formulations of the study drugs: (1) RA: rizatriptan 10 mg (1 tablet) + acetaminophen 1000 mg (500 mg × 2 tablets); (2) P: placebo to match rizatriptan (0 mg × 1 tablet) + placebo to match acetaminophen (0 mg × 2 tablets); (3) A: placebo to match rizatriptan (0 mg × 1 tablet) + acetaminophen 1000 mg (500 mg × 2 tablets); (4) R: rizatriptan 10 mg (1 tablet) + placebo to match acetaminophen 1000 mg (0 mg × 2 tablets). Eligible patients treated a single attack of migraine within 4 h from the onset of pain if the attack met the following criteria: migraine pain was moderate (Grade 2) or severe (Grade 3); migraine pain did not spontaneously resolve; and, migraine was not preceded by any prohibited concurrent medication. If the patient awoke with a migraine headache that met the treatment criteria, the patient could use the study medication within 4 h after awakening. Each patient was to treat a qualifying migraine attack within 2 months after randomization. All patients were to ingest 3 tablets to treat one migraine attack. Patients were allowed to use additional analgesic or anti-emetic rescue medication 2 h after taking study medication for a nonresponsive or recurrent headache. The study consisted of 2 visits: Visit 1 (Prestudy/Randomization) and Visit 2 (Poststudy).

Efficacy and Tolerability Endpoints.—The primary efficacy endpoint was pain relief (Grade 0 or 1) at 2 h after taking study medication. Patients received a diary at Visit 1 that was collected at Visit 2. In the diary, patients subjectively rated headache severity, associated symptoms (phonophobia, photophobia, nausea, and vomiting), and functional disability immediately before ingesting their study medication. Patients continued to rate these factors at 30, 45, 60, and 90 min and

2 and 4 h post-dose. Headache severity was rated on a 4-point scale from Grade 0 to 3: Grade 0 – No headache; Grade 1 – Mild pain; Grade 2 – Moderate pain; Grade 3 – Severe pain. Headache severity (sustained response) was rated between 2 and 24 h post-dose. Functional disability was measured by the level of impairment to the patient's daily activities. It was rated according to the following scale: Grade 0 – Able to perform daily activities; Grade 1 – Daily activities mildly impaired; Grade 2 – Daily activities severely impaired; Grade 3 – Unable to perform daily activities, requires bed rest. Other efficacy measurements were used in support of the primary hypothesis, including 24-h sustained pain relief, defined as pain relief at 2 h with no recurrence (return of headache to moderate or severe) between 2 to 24 h; 24-h sustained pain freedom, defined as pain freedom at 2 h with no return of headache between 2 to 24 h; and no use of any additional antimigraine headache medication (rescue medication) up to 24 h after dosing with study medication.

In the diary, patients also recorded the use of other medication taken 24 h before and 24 h after the use of study medication, any rescue medications taken for migraine headache, including recurrence, and any adverse experience occurring any time after the initial dose of study medication until Visit 2. Reported adverse events were generated spontaneously by the patient.

Patients returned to the study center for the post-study visit within 7 days after treatment of the qualifying migraine headache or 2 months after randomization if they did not treat a qualifying migraine attack. At this visit, an interval medical history and vital signs were taken, a physical examination was performed, and the completed diaries were reviewed with the patient. The occurrence and severity of any adverse event were discussed.

Objectives and Hypotheses.—The primary objective of this study was to compare the efficacy of rizatriptan 10 mg coadministered with acetaminophen 1000 mg, placebo, acetaminophen 1000-mg monotherapy, and rizatriptan 10-mg monotherapy for the acute treatment of migraine, as measured by the percentage of patients with pain relief at 2 h. There were 3 co-primary hypotheses:

1. For the acute treatment of migraine, RA would be superior to P, as measured by the percentage of patients with 2-h pain relief. Provided the above is established, the second co-primary hypothesis would then be assessed.
2. For the acute treatment of migraine, RA would be superior to A as measured by the percentage of patients with 2-h pain relief. Provided the above is established, the third co-primary hypothesis would then be assessed.
3. For the acute treatment of migraine, RA would be superior to R, as measured by the percentage of patients with 2-h pain relief.

The secondary objective was to compare the efficacy of RA, P, A, and R for the acute treatment of migraine, as measured by the percentage of patients with pain relief at 30, 45, 60, 90 min, and 4 h post-dose; 24-h sustained pain relief; pain freedom at 30, 45, 60, 90 min, and 2 and 4 h post-dose; 24-h sustained pain freedom; absence of associated symptoms of phonophobia, photophobia, nausea, and vomiting and functional disability at 2 h post-dose; use of rescue medication; and self-reported adverse events.

Statistical Methods.—The primary efficacy analysis used a modified intention-to-treat (mITT) approach. The mITT analysis included all randomized patients who had at least one pain severity rating within 2 h after the initial dose (ie, after baseline evaluation). It was not necessary to have assessments in the treatment phase carried forward to impute the missing data because only a limited number of values were missing. Statistical analysis was conducted by one of the authors (Imke Janssen) at an independent site not directly involved in the design or implementation of the study.

The primary efficacy endpoint of pain relief (Grade 0 or 1) at 2 h was assessed using a logistic regression model with factors for treatment group and baseline headache severity (moderate or severe). A similar logistic regression model was used for analyzing all other binary outcome measures and for a retrospective exploratory analysis of total migraine freedom, defined as pain freedom as well as absence of photophobia, phonophobia, nausea, and vomiting (limited to the 2 h primary timepoint). Multiplicity of

the 3 co-primary efficacy hypotheses was addressed using a sequential testing procedure with a 2-sided P value $\leq .05$ comparing treatment groups considered statistically significant.

There were no existing data for rizatriptan coadministered with acetaminophen at the time of the study. This study was powered to demonstrate a substantial improvement in efficacy over each of the individual groups. Data on the individual groups were taken from the rizatriptan prescribing information for rizatriptan and placebo and from Lipton et al⁹ for the acetaminophen group. Assuming the percentage of patients achieving pain relief at 2 h would be 95% for RA, 70% for R, 60% for A, and 30% for P, 45 patients per group completing the study would be needed in order to have approximately 86% power to demonstrate the 3 co-primary hypotheses. It was expected that 50 patients per group would be needed to yield 180 patients completing the study, assuming an expected 10% failure rate to treat a qualifying migraine.

All patients treated in the study were included in the safety analysis. The primary safety analysis compared the incidence of adverse events reported after taking study medication and before taking any additional analgesia/antiemetics (rescue medication). Pairwise comparisons were conducted using Fisher's exact test. No multiplicity adjustment was used for the safety analysis.

RESULTS

Patient Accounting and Demographics.—Of the 204 patients screened for the study, 200 were randomized to treatment, and 173 treated a qualifying headache (Fig. 1). The percentage of patients without a qualifying headache varied among treatment groups, but the difference was not statistically significant ($P = .504$). Patients were recruited and enrolled over an approximately 6-month time frame across all the study centers. All 173 patients were included in all analyses.

The majority of patients were female (87.9%) and white (79.2%), and these percentages were similar across treatment groups (Table 1). Ages ranged from 20 to 68 years, with a mean of 43.1 years. No significant difference was found in age, body mass

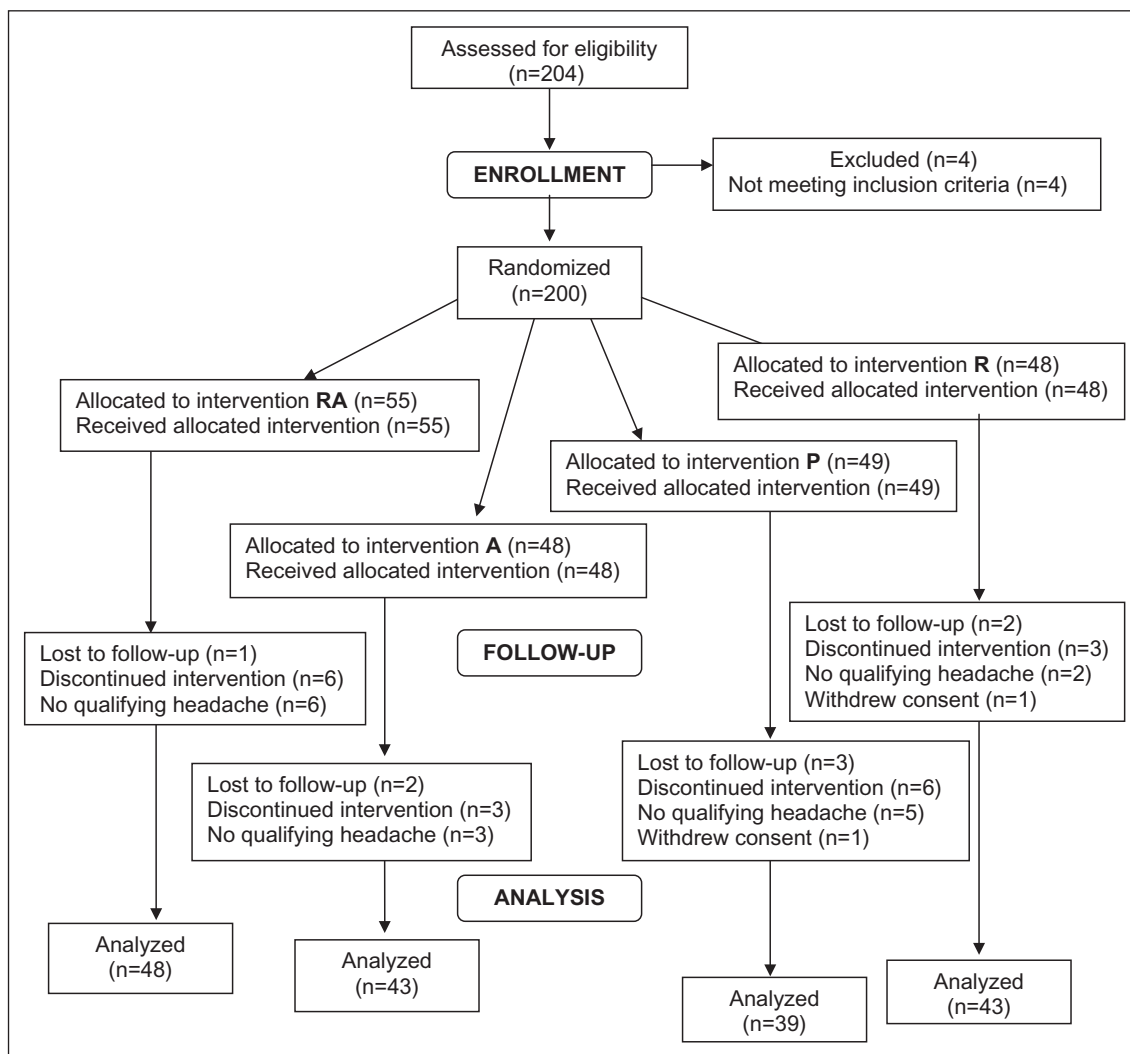


Fig 1.—Patient accounting. A = acetaminophen alone; P = placebo; R = rizatriptan alone; RA = rizatriptan 10 mg + acetaminophen 1000 mg.

index, systolic or diastolic blood pressure, or pulse between the 4 treatment groups.

Analysis.—A total of 71.7% of the 173 patients treating a qualifying headache achieved pain relief after 2 h (Fig. 2). The coadministration of rizatriptan and acetaminophen resulted in 90% of the treated patients having migraine pain relief at 2 h and was statistically superior to both P, with 46% of treated patients responding (odds ratio = 10.87, 95% CI = 3.43, 34.41, $P < .001$), and A alone, with a 70% response rate (odds ratio = 3.71, 95% CI = 1.20, 11.54, $P = .018$). RA was numerically, but not statistically, superior to R, with a 77% 2-h response rate (odds ratio = 2.49, 95% CI = 0.77, 8.08, $P = .128$).

Secondary Analyses.—Additional efficacy parameters of sustained relief from 2 to 24 h, 2-h pain freedom, and 24-h sustained pain freedom are demonstrated in Figure 2. Sixty-two percent of patients in the RA group reported 24-h sustained pain relief. This was statistically superior to P, with a 15% response rate (odds ratio = 8.88, 95% CI = 3.10, 25.47, $P < .001$), but not to A, with a 42% response rate (odds ratio = 2.22, 95% CI = 0.95, 5.18, $P = .064$), or to R, with a 53% response rate (odds ratio = 1.38, 95% CI = 0.59, 3.21, $P = .457$). For the 2-h pain-free endpoint, RA (54%) was statistically superior compared with P (15%, odds ratio = 6.70, 95% CI = 2.35, 19.06, $P < .001$) and A alone (26%, odds ratio = 3.48,

Table 1.—Patient Demographics and Baseline Characteristics

Parameter	All studied patients	RA	R	A	P
N	173	48	43	43	39
Age, mean (SD)	43.1 (10.9)	41.5 (10.3)	44.3 (10.6)	42.0 (11.7)	45.2 (10.9)
BMI, mean (SD)	27.7 (5.9)	28.4 (5.6)	27.7 (6.6)	27.6 (6.0)	26.6 (5.3)
Systolic BP mmHg, mean (SD)	116.1 (11.9)	115.6 (11.9)	114.1 (12.6)	118.3 (12.4)	116.7 (10.8)
Diastolic BP mmHg, mean (SD)	74.4 (8.0)	72.9 (7.8)	73.6 (7.7)	75.8 (8.8)	75.3 (7.6)
Heart rate bpm, mean (SD)	72.6 (5.7)	72.8 (6.6)	73.8 (8.2)	70.6 (8.5)	73.3 (6.4)
Female, N (%)	152 (87.9)	41 (85.4)	35 (83.3)	38 (88.4)	37 (94.9)
Race, N (%)					
White	137 (79.2)	37 (77.1)	33 (76.7)	37 (84.4)	30 (79.0)
Black	27 (15.6)	8 (16.7)	10 (23.3)	4 (9.3)	5 (12.8)
Asian	2 (1.2)	0 (0)	0 (0)	1 (2.3)	1 (2.6)
Hispanic	7 (4.0)	3 (6.3)	0 (0)	2 (4.6)	2 (5.1)

A = acetaminophen alone; BMI = body mass index; BP = blood pressure; P = placebo; R = rizatriptan alone; RA = rizatriptan 10 mg + acetaminophen 1000 mg.

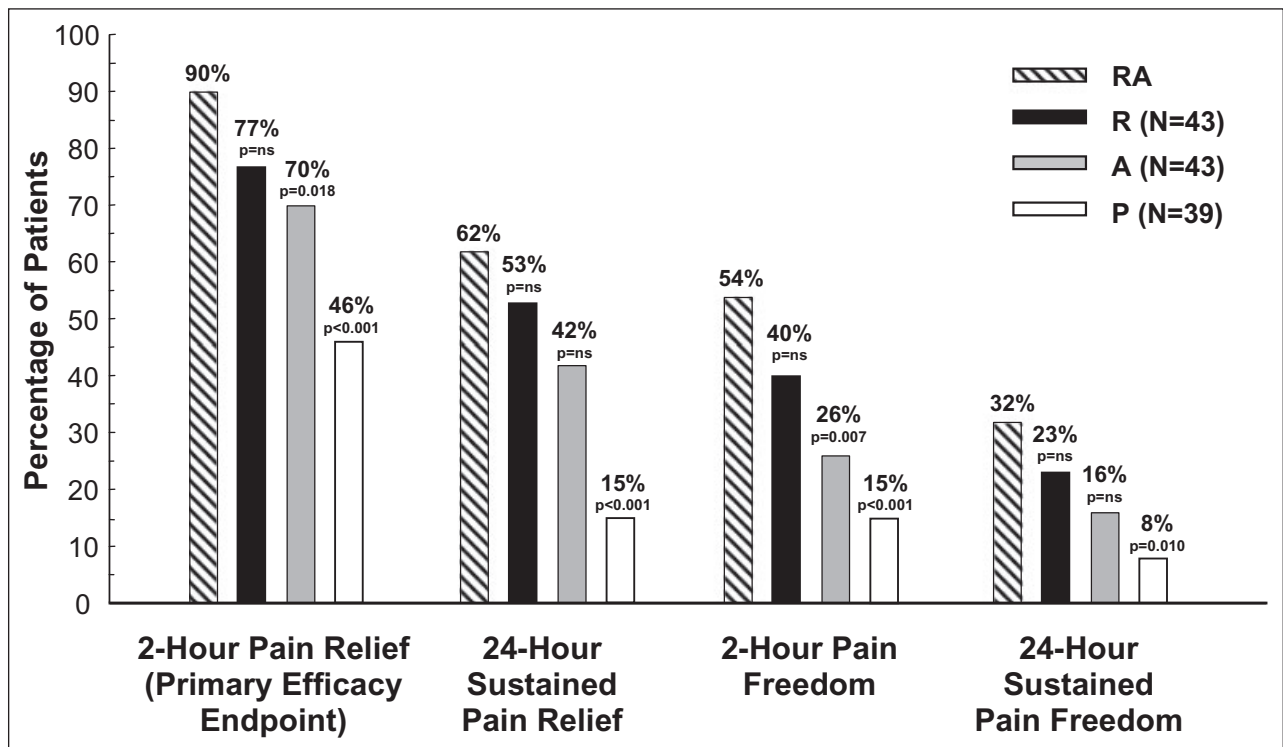


Fig 2.—Pain relief and pain freedom. Bar graph showing the percentage of patients who reported pain relief at 2 h (primary endpoint), sustained pain relief from 2 to 24 h, pain freedom at 2 h, and sustained pain freedom from 2 to 24 h after treatment with the indicated study medications. All *P* values are vs RA and are based on a logistic regression model with factors for treatment group and baseline pain severity. A = acetaminophen alone; P = placebo; R = rizatriptan alone; RA = rizatriptan 10 mg + acetaminophen 1000 mg.

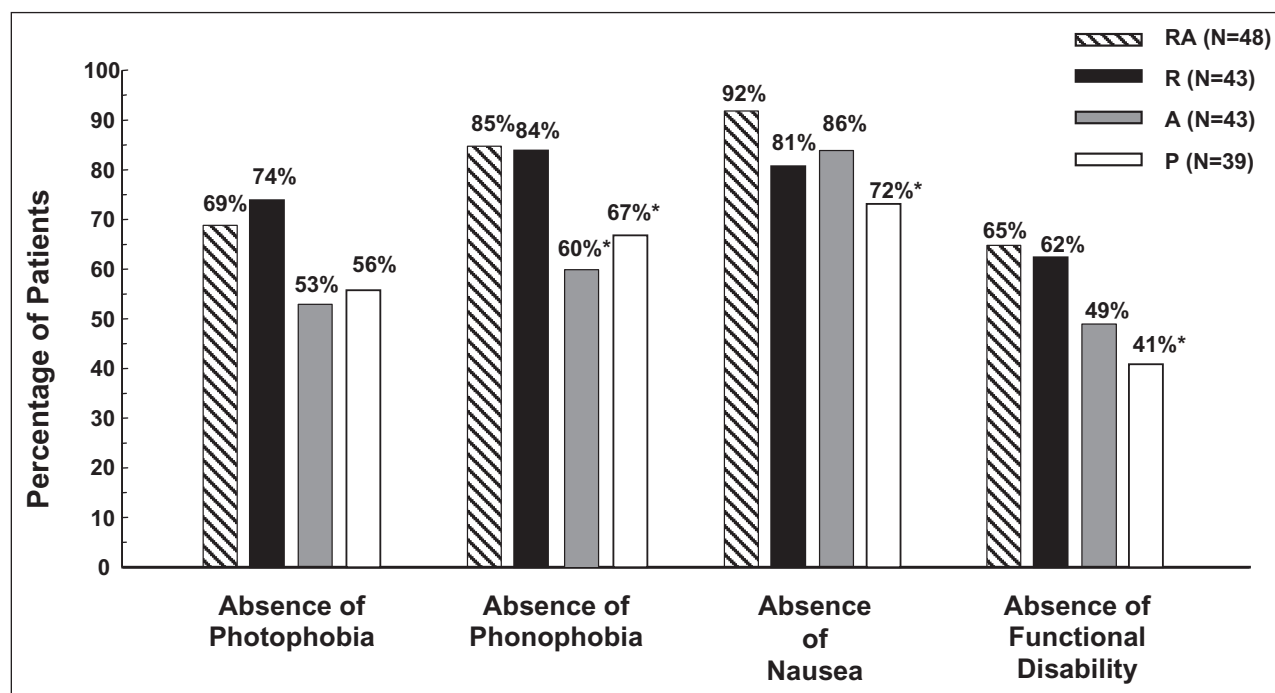


Fig 3.—Absence of associated symptoms and functional disability at 2 h. Bar graph showing the percentage of patients who reported not having the specified associated symptoms or functional disability 2 h after treatment with the indicated study medications. * ≤ 0.05 vs RA, *P* value based on a logistic regression model with factors for treatment group and baseline pain severity. A = acetaminophen alone; P = placebo; R = rizatriptan alone; RA = rizatriptan 10 mg + acetaminophen 1000 mg.

95% CI = 1.41, 8.56, $P = .007$), but only numerically better than R alone (40%, odds ratio = 1.77, 95% CI = 0.76, 4.09, $P = .182$). RA was statistically superior to P for 24-h sustained pain freedom (32% vs 8%, odds ratio = 5.69, 95% CI = 1.51, 21.53, $P = .010$), but was only numerically better than R (23%, odds ratio 1.57, 95% CI 0.61, 4.03, $P = .349$) and A (16%, odds ratio 2.37, 95% CI 0.85, 6.59, $P = .097$). Additional efficacy endpoints are detailed in Figure 3. RA was statistically superior to A for absence of phonophobia (85% vs 60%, $P = .009$) and statistically superior to P for absence of photophobia (85% vs 67%, $P = .039$), absence of nausea (92% vs 72%, $P = .021$), and absence of functional disability (65% vs 41%, $P = .024$).

Retrospective Exploratory Analysis: Total Migraine Freedom.—A retrospective exploratory analysis examined total migraine freedom, defined as pain freedom and absence of all associated symptoms (photophobia, phonophobia, nausea, and vomiting), at 2 h. Consistent with the other efficacy endpoints, RA (44%) was statistically superior compared with P

(15%, $P = .006$) and A alone (21%, $P = .024$), but only numerically better than R alone (37%, $P = ns$) (Fig. 4).

Adverse Events.—No serious adverse events were reported, and no events resulted in discontinuation of study drug. There were no appreciable differences in adverse events between the RA group and any of the other 3 regimens (Table 2). The most frequently occurring side effect in the study was dizziness, reported by 10 patients. The likelihood of having nausea as an adverse event was very similar across treatment groups. Other adverse events were similarly infrequent.

DISCUSSION

The efficacy of rizatriptan has been demonstrated in multicenter, randomized, placebo-controlled studies.¹⁴ In each of these studies, the percentage of patients achieving headache response at 2 h after administration of either R 5 mg (60% to 62%) or 10 mg (67% to 77%) was significantly greater than for those receiving P (23% to 40%). The associated

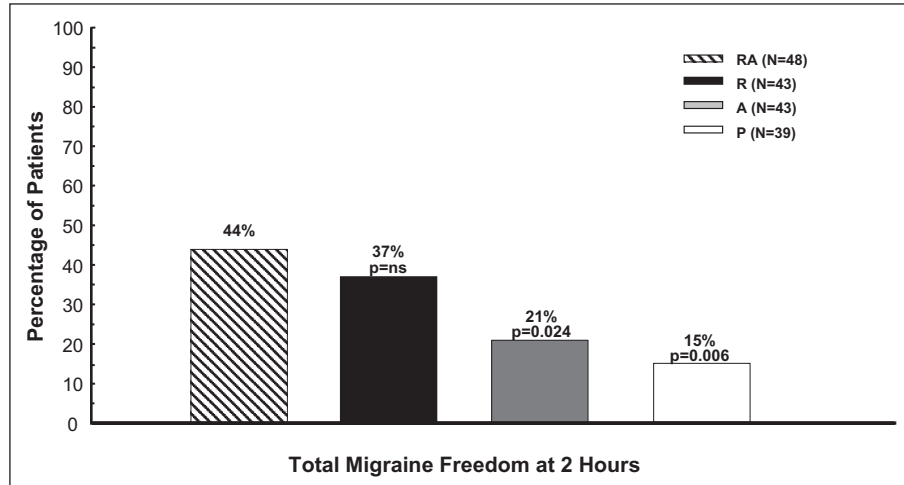


Fig 4.—Total migraine freedom. Bar graph showing the percentage of patients who reported total migraine freedom (pain freedom and absence of all associated symptoms [photophobia, phonophobia, nausea, and vomiting]) at 2 h after treatment with the indicated study medications. All *P* values are vs RA and are based on a logistic regression model with factors for treatment group and baseline pain severity. A = acetaminophen alone; P = placebo; R = rizatriptan alone; RA = rizatriptan 10 mg + acetaminophen 1000 mg.

symptoms of migraine (nausea, photophobia, phonophobia) were also decreased at 2 h in the R groups compared with the P group.

More than 75% of patients with migraine use over-the-counter agents (aspirin, acetaminophen, ibuprofen, naproxen) in the treatment of migraine attacks (personal communication, Richard Lipton, MD. Results from the first year of data from the American Migraine Prevalence and Prevention Study). In a randomized, double-blind, placebo-controlled study by Lipton et al,⁹ acetaminophen

1000 mg was compared with placebo in the treatment of a single acute migraine attack. In addition to the level of pain intensity at 2 h post-dose, other variables were measured, including functional disability, photophobia, and phonophobia. The patients involved in the study did not usually report associated vomiting during their migraine attacks, nor did they require bed rest. In reviewing the differences in baseline pain intensity to intensity at 2 h post-dosing, a significant improvement was noted in the acetaminophen group compared with those receiving placebo. Acetami-

Table 2.—Adverse Events Occurring in More Than 2% of Patients†

	RA (N = 48) n (%)	R (N = 43) n (%)	A (N = 43) n (%)	P (N = 39) n (%)
Patients with 1 or more adverse events	16 (33)	13 (30)	8 (19)	7 (18)
Dizziness	5 (11)	2 (4)	2 (4)	1 (2)
Nausea	3 (5)	1 (2)	0	2 (4)
Dry mouth	0	3 (8)	1 (2)	0
Somnolence	2 (4)	2 (4)	2 (4)	0
Fatigue	2 (4)	2 (4)	1 (2)	0
Chest discomfort	0	0	0	2 (4)

†Reported adverse events are post treatment before use of rescue medication.

A = acetaminophen alone; P = placebo; R = rizatriptan alone; RA = rizatriptan 10 mg + acetaminophen 1000 mg.

nophen was significantly more effective than placebo in reducing associated photophobia, phonophobia, and functional disability. The drug has an excellent safety profile and is well-tolerated.¹⁵

In the current study, the first 2 of the 3 co-primary hypotheses were met. For pain relief at 2 h, coadministration of RA was significantly better than P and A monotherapy, but not significantly different from R monotherapy, although numerically it was superior. As this was the first time the combination of R and A for migraine had been studied, it was difficult to accurately predict the differences between study arms to power the study. The sample size of this study only allowed for differences of 16% or greater to be declared as statistically significant when compared with the RA 90% pain relief rate. A larger study may have shown a significant difference between RA and R.

Additionally, this study was conducted in a “registration-type” trial among migraineurs, which was a deliberate departure from current medical practice of treating migraine while the pain is still mild and the duration of migraine remains less than 1 h. The use of acetaminophen to treat migraine that is typically disabling and has met IHS criteria for migraine has not been studied previously, but rather it has been examined in a model used in the earlier study by Lipton et al⁹ with patients being less severely affected by their migraine. By using early intervention models, one would expect to observe greater efficacy than for treating the headache once it becomes moderate to severe.

The fairly large placebo response can be a factor when the primary endpoint in moderate to severe initial treatment trials is pain relief.¹⁶ The placebo rate may also increase with the number of active treatment arms. This issue is not as significant when a more aggressive endpoint is used, such as pain-free and sustained pain-free. In review of the safety data, it should be noted that no increase in adverse events was observed in the RA group vs either R or A.

Recently, the US Food and Drug Administration (FDA) has set a higher hurdle for the approval of new acute migraine medications. The FDA now requires that these new agents establish efficacy not only for pain relief or pain freedom, but also for the relief of the associated symptoms of phonophobia, photopho-

bia, and nausea. In the current study, RA achieved statistical significance over P only for 2-h pain relief, phonophobia, and nausea, but not for photophobia, although it is recognized that this study was not powered to establish efficacy across all of these endpoints. A composite endpoint, migraine freedom, defined as pain freedom and absence of all associated symptoms (photophobia, phonophobia, nausea, and vomiting), has recently been used in clinical trials to address this higher FDA efficacy hurdle.¹⁷ In the current study, an exploratory retrospective analysis of total migraine freedom at 2 h showed that RA was superior to both P and A, but it failed to show superiority vs R, which is consistent with the results of the primary analysis of pain relief at 2 h.

CONCLUSION

The use of combination therapies in treating migraine is not new. Ergotamine tartrate was typically prescribed as a combination agent with caffeine and other adjunctive therapeutic agents. In more recent times, clinical trials with a combination of sumatriptan and naproxen have demonstrated significant clinical efficacy. The results of this study are consistent with the emerging recognition of multi-mechanism therapy in the acute treatment of migraine. This may be of importance for optimizing clinical outcomes for patients with migraine not merely by early treatment paradigms, but by treating migraine via multiple mechanisms. The concerns regarding the use of the NSAIDs and their effect on cardiovascular safety need to be considered while the evidence on this issue evolves. The demonstrated added benefit from another class of analgesic without the safety concerns of the nonsteroidal drugs combined with a triptan offers new avenues for migraine therapy. The limitations of this study emphasize the need for future studies to include a larger number of patients appropriately powering to study all 3 active components vs placebo for efficacy and tolerability as well as early intervention studies using the coadministration of rizatriptan and acetaminophen.

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