A Combination of Riboflavin, Magnesium, and Feverfew for Migraine Prophylaxis: A Randomized Trial

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Objective.—To determine the efficacy for migraine prophylaxis of a compound containing a combination of riboflavin, magnesium, and feverfew.

Background.—Previous studies of magnesium and feverfew for migraine prophylaxis have found conflicting results, and there has been only a single placebo-controlled trial of riboflavin.

Design/Methods.—Randomized double-blind placebo-controlled trial of a compound providing a daily dose of riboflavin 400 mg, magnesium 300 mg, and feverfew 100 mg. The placebo contained 25 mg riboflavin. The study included a 1-month run-in phase and 3-month trial. The protocol allowed for 120 patients to be randomized, with a preplanned interim analysis of the data after 48 patients had completed the trial.

Results.—Forty-nine patients completed the 3-month trial. For the primary outcome measure, a 50% or greater reduction in migraines, there was no difference between active and "placebo" groups, achieved by 10 (42%) and 11 (44%), respectively ($P = .87$). Similarly, there was no significant difference in secondary outcome measures, for active versus placebo groups, respectively: 50% or greater reduction in migraine days (33% and 40%, $P = .63$); or change in mean number of migraines, migraine days, migraine index, or triptan doses. Compared to baseline, however, both groups showed a significant reduction in number of migraines, migraine days, and migraine index. This effect exceeds that reported for placebo agents in previous migraine trials.

Conclusion.—Riboflavin 25 mg showed an effect comparable to a combination of riboflavin 400 mg, magnesium 300 mg, and feverfew 100 mg. The placebo response exceeds that reported for any other placebo in trials of migraine prophylaxis, and suggests that riboflavin 25 mg may be an active comparator. There is at present conflicting scientific evidence with regard to the efficacy of these compounds for migraine prophylaxis.

Key words: migraine, prophylaxis, natural supplements, magnesium, riboflavin, feverfew, placebo

Abbreviations: HMO health maintenance organization, IHS International Headache Society

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A variety of "natural supplements" have been promoted as having efficacy for migraine prophylaxis. Among the most commonly recommended supplements are riboflavin, magnesium, and feverfew, an extract from a plant belonging to the chrysanthemum family. Each of these compounds has a theoretical mechanism of effect on migraine, and has had at least one double-blind placebo-controlled trial that demonstrated efficacy.

A mitochondrial dysfunction causing impaired oxygen metabolism may play a role in migraine pathogenesis.[1] Riboflavin was piloted for migraine after it was found to improve the clinical condition of patients with mitochondrial myopathies.

Numerous possible roles for magnesium in migraine pathogenesis have been suggested. Magnesium concentration has an effect on serotonin receptors, nitric oxide synthesis and release, and a variety of other migraine-related receptors and neurotransmitters.[2] Twenty-nine percent (29%) of patients with "various headache syndromes" had low levels of ionized magnesium, and during an acute migraine attack, 50% were found to have a low level.[2]

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The active ingredient in feverfew is thought to be parthenolide, which is known to inhibit platelet aggregation and the release of serotonin from platelets, as well as inhibiting prostaglandin biosynthesis. However, whole leaf preparations of feverfew may have effects beyond that of parthenolide.[3]

Clinical studies of these supplements have involved small populations, used different methodologies, and had conflicting results (see section "Discussion"). It is likely that different patients may have different biochemical bases for their migraines. Thus, it is reasonable to consider that a combined product may have efficacy for a larger percentage of the population than any of the individual ingredients.

METHODS

The study was conducted at two suburban hospital-based headache clinics, belonging to the same health maintenance organization (HMO). Patients were recruited by flyers, which were posted in the medical center, by an announcement in the health plan's newsletter, and by announcement at the educational sessions of the headache clinics.

Inclusion criteria were: (1) migraine with or without aura, as defined by the International Headache Society (IHS) criteria; (2) history of migraine for at least 1 year; (3) migraine frequency two to eight episodes/month (or at least 2 headache days/month); (4) age 18 to 65 years; and (5) the patient could clearly distinguish migraine from any other headache.

Exclusion criteria were: (1) frequent tension or other headaches (total number of headache days >15/month); (2) daily or near-daily use of analgesics (>15 days/month); (3) patients who had failed more than three previous trials of adequate prophylaxis (including tricyclic antidepressants, β-blockers, calcium channel blockers, valproic acid, gabapentin); (4) pregnancy or intent to become pregnant. Medical exclusions were limited to uncontrolled hypertension and active kidney disease or liver disease. Patients who were already on other prophylaxis were included if the dose had been stable for at least 3 months. Patients who were already using feverfew were excluded. Patients were allowed to take a general multivitamin, which contained minimal amounts of riboflavin or magnesium.

Patients were asked to keep a headache diary for a 1-month (30 day) run-in period. The severity of migraines was rated "0" (none), "1" (mild), "2" (moderate—activity impaired), or "3" (severe—unable to function). The diary documented frequency of migraines, duration (in days), severity, and use of triptan medication. Patients returned after 1 month for review of the diary. Patients who had severity "1" migraines were asked to distinguish these headaches from tension or other headaches. Patients were asked to record the number of dosages of acute medication taken and the response of the headache to medication after 2 hours. A measure of migraine severity was defined as: (sum of migraine days $\times$ rated severity of each day)/number of migraine days.

Patients who successfully completed the run-in month and had at least 2 migraine days were randomized to receive either study drug or placebo, and received a 1-month supply. Patients were followed up in the clinic monthly for review of diary and dispensing of another month's medication. They were contacted by telephone in between visits every 2 weeks.

Study Drug and Placebo.—Two caplets of the study drug provide magnesium 300 mg (1:1 ratio of magnesium citrate and oxide), riboflavin 400 mg, and feverfew 100 mg (standardized to 0.7% parthenolide). Because riboflavin causes a bright color of urine, which could have allowed patients to suspect they were receiving active medication, 25 mg of riboflavin was added to the placebo to cause a similar color change. It was thought that this amount of riboflavin would not have clinical activity. Patients were told that they might notice a discoloration of the urine, whether they were receiving active drug or placebo.

Data Analysis.—Based on an anticipated 60% response rate to the study drug, and a 30% placebo response, it was calculated that to detect a difference with α equal to the traditional 0.05 level, 48 subjects per group would be required to have a power of 80%. This calculation allowed for a midpoint evaluation of the data after a total of 48 patients have completed the study. To allow for dropouts and loss to follow-up, 120 patients were to be randomized.

The primary outcome measure was defined as the percentage of patients who achieved a 50% or greater decrease in the number of migraine attacks during the

third month, compared to the run-in month. Secondary outcome measures were: the percentage of patients who achieved a 50% or greater reduction in migraine days, and the overall difference between the groups at 3 months in migraine attacks, migraine days, migraine severity, doses of triptan medication, and days of tension-type headache.

The study protocol was approved by the Institutional Review Board of the HMO, and all patients signed informed consent.

RESULTS

Fifty-seven patients met inclusion criteria and entered the run-in phase. Five patients were excluded before randomization because of: medical or surgical complications during the run-in phase (3), or inability to complete the diary (2). Fifty-two patients were randomized to receive active medication or placebo, and 49 completed the 3-month protocol. Three patients dropped out after the first month because of: other medical problems (1), not following protocol (1), and headaches worsening (1). Baseline demographics, headache frequency, and severity are shown in Table 1.

For the primary outcome measure, a 50% or greater reduction in migraines, there was no difference between active and placebo groups, achieved by 10 (42%) and 11 (44%) patients, respectively ($P = .87$) (Table 2 and Figure). Similarly, a 50% or greater reduction in migraine days was seen in 8 (33%) and 10 (40%) patients, respectively ($P = .63$).

Although there was no difference between groups, there were statistically significant reductions for both active and placebo groups, respectively, compared to baseline, for number of migraines (5.0 to 3.2, 5.0 to 3.3, $P < .0001$ and $P = .0006$, respectively), migraine days, (7.8 to 5.8, 7.7 to 5.9, $P = .04$, $P = .07$, respectively), and migraine index (13.3 to 10.4, 14.1 to 9.5, $P = .10$, $.0006$). In addition, mean headache severity and number of tension headache days improved for the placebo group ($P = .04$, $.01$, respectively).

Because of the high placebo response rate, samples of medication from five patients who returned unused medication were sent to the manufacturing company for analysis. The contents of all five were found to correspond to the appropriate category of study drug or placebo. Only the supervising statistician and the sponsoring company were aware of which study patient numbers corresponded to study drug or placebo.

Because the study protocol was designed for an interim analysis, with a provision to terminate the study if active drug showed either very negative or very positive results, the study was terminated after the interim analysis.

DISCUSSION

The study drug, a combination of riboflavin, magnesium, and feverfew, showed no advantage compared to a 25-mg riboflavin "placebo" over the 3-month study period. In the active product, the daily doses of riboflavin and feverfew are comparable to doses used in previous successful trials, although the magnesium

Table 1.—Baseline Demographics and Headache Characteristics During Run-in Month

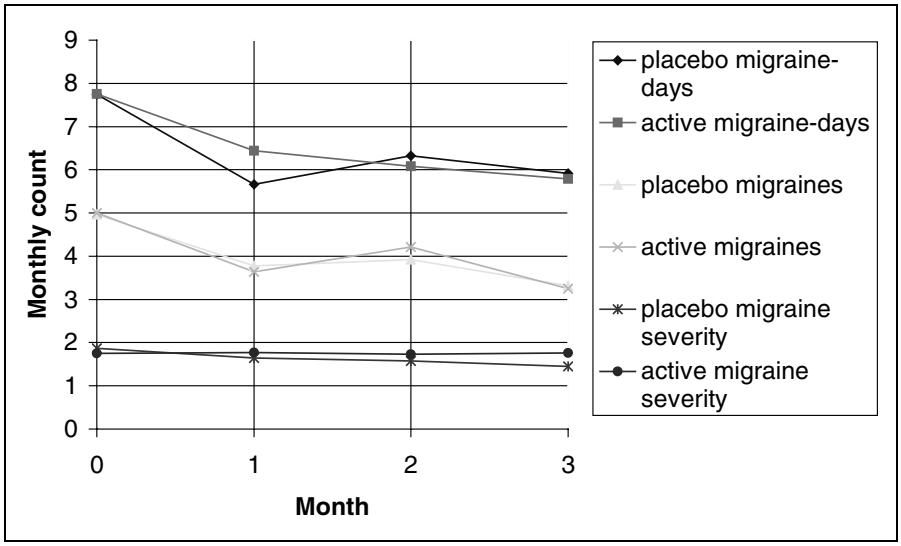
	Placebo			Active			
	N	Mean	Std. Dev.	N	Mean	Std. Dev.	*P*
Age	28	46.6	10.4	29	47.0	8.2	.88
Gender (% males)	28	10.7%	—	29	6.9%	—	.62
Prophylaxis (% taking)	28	25.0%	—	29	37.9%	—	.23
Migraines	27	5.0	1.9	29	5.0	1.6	.94
Migraine days	27	7.7	3.4	29	7.8	3.6	.98
Migraine severity	27	1.9	0.4	29	1.8	0.5	.34
Migraine index	27	14.1	6.8	29	13.3	6.1	.66
Tension-type headache days	27	1.2	1.9	29	1.8	2.5	.28
Triptan doses/month	27	4.2	5.6	29	3.3	3.7	.49

Table 2.—Responders and Change in Outcome Measures at 3 Months Compared to Baseline (outcome measures are monthly frequency)

	Placebo (N = 25)		Active (N = 24)		*P*
Responders (50% decrease)					
Migraines	11 (44%)		10 (42%)		.87
Migraine days	10 (40%)		8 (33%)		.63
	Mean	Std. Dev.	Mean	Std. Dev.	*P*
Change from baseline					
Migraines	−1.68	2.14	−1.79	1.47	.83
Migraine days	−1.56	4.16	−2.04	4.47	.70
Headache index	−4.56	5.76	−2.88	8.12	.40
Headache severity	−0.36	0.82	0.02	0.66	.09
Tension-type headaches	−0.84	1.60	−0.04	3.57	.31
Triptan doses	0.52	3.62	−0.21	2.62	.43

dose is lower: previous trials typically used 450 to 600 mg.

The placebo response is higher than that reported in any previous prophylactic trial. Van der Kuy and Lohman conducted a meta-analysis of placebo response in migraine prophylaxis trials.[4] A reduction of attack frequency of 50% or more (responders) was seen in 23.5 ± 8.0% (95% CI: 18.3% to 28.8%) of placebo groups compared to 45.5 ± 15.5% (95% CI: 37.4% to 53.6%) in the active groups. The range in placebo groups was 14% to 34%. Migraine attack frequency was reduced 16.8 ± 12.7% (95% CI: 10.9% to 22.6%) in the placebo groups and 41.8 ± 11.7% (95% CI: 36.9% to 46.6%) in the active groups, with the range for placebo groups −7% to 39%. The present study found a placebo responder rate of 44%, higher than that reported in any previous prophylactic trial, and near the mean rate for active products. Mean attack frequency was reduced 34%, near the upper limit previously reported.



Migraines, migraine days, and mean migraine severity at run-in and months 1 through 3 for placebo and study drug.

The previous report of riboflavin for migraine prophylaxis utilized a dose of 200 mg twice a day. This study randomized 55 patients, and found a 50% responder rate of 56% for active drug versus 9% placebo for attack frequency, 59% versus 15% for migraine days, and 41% versus 8% for migraine index.[1] Significant improvement was seen at 1 month and 3 months but not at 2 months. β-carotene was used to mask the placebo product.

In case reports of rare neurologic syndromes, effective daily doses of riboflavin have ranged from 100 mg (NADH-CoQ reductase deficient myopathy)[5] to 300 mg (MELAS syndrome).[6]

Randomized placebo-controlled trials of magnesium have shown conflicting results, possibly in part due to different dosages and formulations. One study of 81 patients used a 600 mg formulation of magnesium dicitrate in the form of a water-soluble granular powder. Patients who received magnesium showed a 42% decrease in attack frequency, compared to 16% for placebo, after 12 weeks.[7] A second study of 69 patients used magnesium-L-aspartate-hydrochloride-trihydrate, also as a granular powder, equivalent to 486 mg magnesium daily. After 12 weeks, there were 10 (29%) responders in each group.[8]

A systematic review of the literature on feverfew found five trials that were randomized, double-blind, and placebo controlled.[9] One study evaluated only the effect of withdrawal from feverfew (finding an increase of headache),[10] and another studied its effect on serotonin uptake and platelet activity (no effect), as well as efficacy.[11] Of the remaining three studies, all using crossover designs, two showed "efficacy" and one did not. Palevitch et al[12] showed reduced headache severity and associated symptoms, but surprisingly, no results were reported for the actual number of headache attacks. Murphy et al used a 4-month treatment period with a crossover design without any washout period. They reported a 24% reduction in attack frequency and other global measures of efficacy. However, improvement in the number of attacks was significant only after 4 months and only in the first treatment cycle (ie, not in the crossover period).[13] More recently, a double-blind randomized placebo-controlled dose-response study failed to show a significant prophylactic effect, or a dose-response effect, of an extract of feverfew, containing 2.0, 6.25, or 18.75 mg.[14]

To evaluate whether participation in our Headache Clinic may have contributed to the high placebo response, we retrospectively determined that seven placebo patients and five study drug patients had participated in the Headache Clinic before participation in the research study. This factor was not felt to contribute to the reported results.

LIMITATIONS OF THE STUDY

The results of the study show that the effect of riboflavin 25 mg is comparable to that of the study drug. Whether this effect is an active effect as opposed to a placebo effect is not resolved. Twenty-five percent of placebo patients and 38% of study drug patients ($P = .23$) were taking prophylaxis. The interaction of the combination product with other preventive therapies is unknown. It is further possible, but unlikely, that there is an undescribed interaction of the three ingredients in this combination with each other that could be preventing the beneficial effects reported from previous studies. Pill counts were not performed, although it is likely that patient compliance would be at least comparable to what would be expected in a nonstudy context. Finally, the study period of 3 months may be too short to show benefit.

CONCLUSION

A combination product providing a daily dose of riboflavin 400 mg, magnesium 300 mg, and feverfew 100 mg, showed an effect comparable to that of a placebo which contained 25 mg of riboflavin. The placebo responder rate is higher than that previously reported in any migraine prophylaxis trial. These results should be interpreted in context of previous studies of the individual compounds, which suggest a metabolic effect for doses of as little as 100 mg of riboflavin, different results for different doses and formulations of magnesium, and conflicting results for feverfew. Further trials, which include standardization of products, and dose-response curves will be

necessary to resolve the role of these agents for migraine prophylaxis.

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