High-dose riboflavin for prophylaxis of migraine

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Schoenen J, Jacquy J, Lenaerts M. Effectiveness of high-dose riboflavin in migraine prophylaxis. A randomized controlled trial. *Neurology* 1998;50: 466-70.

Research question

Is high-dose riboflavin (vitamin B_2) effective for prophylaxis of migraine?

Type of article and design

Randomized, double-blind, placebo-controlled clinical trial using a two-parallel group design.

Relevance to family physicians

Migraine is a serious problem in terms of morbidity and health care costs. The 1998-1999 Statistics Canada National Population Health Survey[1] reports that 7.9% of Canadians older than 12 have been diagnosed with migraine headaches. Women are more affected than men at a ratio of 3:1 (11.7% vs 3.8%); this difference is most pronounced between age 25 and 39. Those who have migraines are more likely to have other chronic conditions, such as allergies, asthma, arthritis or rheumatism, hypertension, and depression. People who have had a major depressive episode are nearly three times as likely to have migraine as those who have not (20.4% vs 7.3%).

Recent guidelines[2] recommend migraine prophylaxis if patients have more than two attacks monthly (or fewer attacks that cause severe disability), if abortive agents are ineffective or contraindicated, or if fewer headaches would improve their lives. β-Blockers are first-line therapy for prevention; amitriptyline is second. The efficacy of calcium channel blockers is controversial, but they are frequently used. Some anticonvulsants might be useful, but their safety is not established. Use of feverfew is controversial, but some evidence supports its use for migraine prophylaxis. Methysergide and phenelzine are considered last resort because of potentially serious side effects.

The theoretical basis for using riboflavin is its ameliorating effect on the mitochondrial dysfunction that might be involved in the pathophysiology of migraine. A previous study of 49 patients treated with 400 mg daily of riboflavin showed a mean global improvement of 68.2%.[3]

In another non-randomized trial, 26 patients with migraine received 4 months' migraine prophylaxis with either riboflavin or β-blockers (metoprolol or bisoprolol). Clinical improvement was seen with both treatments. Based on auditory evoked cortical potential responses, which were assessed before and after treatment, the authors concluded that β-blockers and riboflavin act through different pathophysiologic mechanisms.[4]

Overview of study and outcomes

In this study, the effectiveness of high-dose riboflavin (400 mg daily) was compared with placebo for migraine prophylaxis. Eighty patients with migraine (aged 18 to 65 years), who met the International Headache Society's (IHS) diagnostic criteria for migraine[5] with or without aura for at least 1 year, were enrolled at six centres in Belgium and Luxembourg. Additional inclusion criteria were two to eight attacks monthly, 5 or fewer days between headaches monthly, no excessive consumption of analgesic or ergotamine, and no serious organic or psychiatric disease.

The study began with a 1-month run-in placebo period for all study candidates. During this month, baseline migraine frequency was established for later comparison, and 25 patients with no headaches during the baseline month were excluded. The remaining 55 patients were randomized to 3 months' treatment with riboflavin (400-mg capsules) (28 patients) or placebo (27 patients). Patients and

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investigators were blinded. During the 3-month treatment period, patients kept diaries of migraine attacks: headache severity using a 4-point scale (0—no pain, 1—mild, 2—moderate, 3—severe), nausea and vomiting, duration of headache in hours, and type and amount of acute headache treatment. Compliance was assessed by capsule count, and patient diaries were reviewed monthly. Patients were queried about possible adverse events.

Primary outcome measure was difference between groups in change in migraine attack frequency (number of migraines monthly) during month 4 compared with migraine attack frequency during the baseline month. Secondary outcome measures included reduction of number of migraine headache days; mean migraine severity; mean migraine duration; migraine index (headache days plus mean severity); number of days of nausea and vomiting; and mean number of tablets, suppositories, or injections taken daily. The proportion of patients with at least a 50% improvement was defined for each of headache days, attack frequency, and migraine index. Effectiveness was reported as number needed to treat (NNT) for each of those three parameters and number needed to harm (NNH). Statistical analysis was completed on an intention-to-treat basis.

Results

Baseline characteristics of the groups were similar. In both groups, there were more women (78%); average age was 36 years. Most study patients (78%) had predominantly migraine without aura, had 3.75 migraines monthly, and had headaches lasting a mean of 32 to 36 hours. Average duration of disease was around 13 years.

There was a statistically significant reduction in migraine attack frequency (primary outcome) in the riboflavin group compared with placebo. Migraine attack frequency was decreased in each of the treatment months compared with the baseline month ($P < .01$ for all 3 months). Patients in the riboflavin group had an average of two fewer migraines monthly ($P = .0001$). In the final month, the riboflavin group also had the following statistically significant improvements: three fewer migraine days ($P = .0001$), decreased severity on the 4-point scale ($P = .031$), decreased migraine index ($P = .031$), decreased migraine duration ($P = .018$), and fewer days with nausea or vomiting ($P = .016$). There was no difference in medication use.

When data from all months of intervention were pooled, difference in attack frequency ($P = .005$), headache days ($P = .012$), and migraine index ($P = .012$) were the only variables that remained statistically significant. In the placebo group, there was no significant change in any outcome variable.

The NNT to achieve at least 50% improvement was 2.3 for headache days, 2.8 for attack frequency, and 3.1 for migraine index. The NNH, based on a single patient who reported diarrhea, was 33.3 for riboflavin. Compliance was excellent, with a mean of 3.5 capsules returned by patients completing the trial. Few adverse events were reported.

Analysis of methodology

Study methodology is generally strong. The study was prospective, randomized, double blinded, and placebo controlled. Subjects are representative of typical primary care populations in Canada. Characteristics of patients in treatment and placebo groups were similar at the start of the trial. All patients were accounted for; five patients failed to complete the study. Protocol adherence was assessed by capsule count as an objective measure. The study used intention-to-treat analysis. Appropriately, the Mann-Whitney U test was used to detect differences between groups. Finally, despite the small number of subjects enrolled, clinically and statistically significant results were found.

The study design has several limitations. Few comorbidities were reported: they would be helpful for assessing relevance to typical family practice populations and, in a larger study, for controlling for potential confounders. Although reported adverse effects were few, detailed diaries of side effects were not kept. Study outcomes are clinically relevant. While it was appropriate to use self-reported outcomes for a clinical problem without objective findings, an objective measure of functional impairment, such as lost workdays, would have strengthened the results. Finally, a longer study period would clarify the efficacy and side-effect profiles for longer durations of therapy.

Application to clinical practice

This study is important to family practitioners because the intervention has favourable and clinically relevant results, is relatively benign and inexpensive, and is applicable to patients with migraine in family practice. The effect of riboflavin on migraine begins at 1 month, but was maximal at 3 months, when this study ended. The most pronounced effect is shorter migraine attacks followed by fewer migraine attacks. Treatment with high-dose riboflavin is also associated with modest improvement in headache severity, less consumption of antimigraine drugs, and fewer

migraine-associated gastrointestinal symptoms, compared with placebo.

To maximize compliance, prophylaxis must be safe, well tolerated, and inexpensive. Although valproate prophylaxis has a NNT of 1.6 and riboflavin has 2.3, valproate also has a NNH of 2.4 while riboflavin has 33.3.[6] Riboflavin's main advantage is its excellent efficacy and side-effect profile.

Bottom line

- High-dose riboflavin (400 mg) is effective for migraine prophylaxis (NNT is 2.8 to decrease attack frequency by 50%).
- High-dose riboflavin appears to be safe and to have relatively few adverse effects.

Points saillants

- La riboflavine à forte dose (400 mg) est efficace pour la prévention de la migraine (NNT est de 2,8 pour réduire la fréquence des épisodes de 50%).
- La riboflavine à forte dose semble sans risque et n'a pas beaucoup d'effets secondaires indésirables.

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