European Journal of Neurology 2004, 11: 475–477

High-dose riboflavin treatment is efficacious in migraine prophylaxis: an open study in a tertiary care centre

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Keywords:
clinical trial, migraine, preventive treatment, vitamin B2

Received 25 September 2003
Accepted 26 December 2003

The aim of this study was to investigate the efficacy of riboflavin for the prevention of migraine. An open label study was performed in a specialized outpatient clinic. Patients received 400 mg riboflavin capsules per day. Headache frequency, duration, intensity and the use of abortive drugs were recorded at baseline and 3 and 6 months after treatment. Headache frequency was significantly reduced from 4 days/month at baseline to 2 days/month after 3 and 6 months ($P < 0.05$). The use of abortive drugs decreased from 7 units/month to 4.5 units/month after 3 and 6 months of treatment ($P < 0.05$). In contrast, headache hours and headache intensity did not change significantly. We could demonstrate a significant reduction of headache frequency following riboflavin treatment. In addition, the number of abortive anti-migraine tablets was reduced. In line with previous studies our findings show that riboflavin is a safe and well-tolerated alternative in migraine prophylaxis.

Introduction

The prophylactic treatment of migraine remains challenging. A host of drugs is available for preventive migraine treatment but their use is often limited by side-effects and the lack of tolerability (Diener *et al*., 2001). In addition, little is known about the mechanisms by which prophylactic agents exert their effects on migraine prevention.

Migraineurs with or without aura show an interictal reduction of phosphorylation potential in brain and muscle (Barbiroli *et al*., 1992; Montagna *et al*., 1994). Riboflavin is a precursor for two coenzymes, flavin mononucleotide and flavin adenine dinucleotide. These are involved in the transfer of electrons in oxidation–reduction reactions. Patients with mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes (MELAS) also show a reduced mitochondrial energy metabolism and experience headaches similar to headaches in migraine. In these subjects riboflavin treatment alleviated symptoms (Arts *et al*., 1983). Based on the hypothesis that among others an impaired oxygen metabolism may contribute to the development of migraine attacks Schoenen *et al*. (1994, 1998) investigated the efficacy of riboflavin treatment in migraine. An open pilot study and a subsequent randomized controlled trial demonstrated the efficacy of high-dose riboflavin treatment (400 mg/day) in migraine prophylaxis. The pilot study was performed as a single-centre study, whilst the subsequent study was a multi-centre study. Considering the low number of adverse events of high-dose riboflavin treatment in comparison with other prophylactic agents (e.g. metoprolol caused side-effects in 39.3% of the patients; Diener *et al*., 2001), riboflavin appears to be an alternative choice for migraine prophylaxis.

We performed an open label study to determine the effect of riboflavin in a specialized headache outpatient clinic (tertiary care).

Patients and methods

Twenty-three patients were included in this study. All patients were recruited from our tertiary care outpatient clinic. Inclusion criteria were: diagnosis of migraine with or without aura according to the criteria of the International Headache Society (Headache Classification Committee of the International Headache Society, 1988), age 20–65 years, headache frequency 2–8 attacks/month in the last 6 months prior to the study. Exclusion criteria were pregnancy or lactation, presence of symptomatic or medication overuse headache, other primary headaches if patients could not differentiate between migraine and other headaches. Patients were not allowed to take other prophylactic medication for the duration of the study and 3 months before the study. Informed consent was obtained prior to enrolment to this study. Patients' characteristics are summarized in Table 1.

After enrolment a 4-week baseline period was followed by a 3-month treatment period, which could be extended by another 3-month treatment period.

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Table 1 Characteristics of patients

Number of patients	23
Age (years, mean ± SD)	52.09 (10.05)
Number of women	19 (82.61%)
Diagnosis	
Migraine with aura	6 (26.09%)
Migraine without aura	17 (73.91%)
Number of previous prophylactic treatments	
0	5
1	5
>2	12

Riboflavin (400 mg) capsules per day were administered. Patients kept a headache diary and recorded the following: number and duration of attack, headache intensity on a 5-point scale (0, no pain; 1, mild; 2, moderate; 3, severe; 4, very severe; 5, unbearable), quality and distribution of pain, concomitant symptoms (e.g. nausea and vomiting, photophobia), and abortive medication. After the treatment period the patients returned the diary for evaluation. At this point patients could extend the treatment period for three more months.

Primary end-point was the reduction of the attack frequency in the third month of treatment; secondary end-points were reduction of attack duration in hours in the third month of treatment, reduction of intake of abortive medication used for acute migraine treatment in the third month of treatment, reduction of intensity of attacks in the third month of treatment.

Statistical analysis was performed on an intention-to-treat basis. Data from patients excluded from the study after a treatment period of at least 1 month were kept forward using the last-value-carried-forward method. For descriptive statistics of data the median, the 25 and 75% percentile and the lowest and highest values were calculated and displayed in boxplots (Fig. 1).

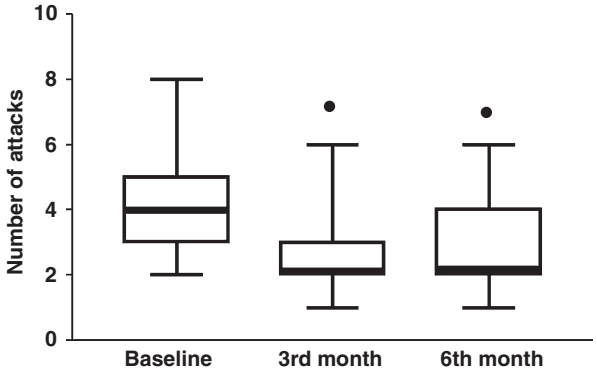

Figure 1 Attack frequency (median ± SD) was reduced after 3 and 6 months of riboflavin treatment ($n = 23$; $P < 0.05$ after 3 and 6 months; dots are 1.5- and 2-fold of median, same patient in month 3 and 6); thick lines illustrate the median.

Results

With respect to the primary end-point, median attack frequency was reduced from 4 attacks/month (range 3–5) in the baseline period to 2 attacks/month (range 2–3, $P < 0.001$) after 3 months of treatment. Attack frequency remained low at 2 attacks/month after 6 months of riboflavin treatment (median 2, range 2–4, $P = 0.005$).

Eighteen patients used exclusively triptans to abort migraine attacks whereas in 13 subjects triptans and analgesics (OTC) were used. In the third month of treatment the intake of abortive anti-migraine tablets was significantly reduced compared with baseline. Patients used 7 tablets/month at baseline, which was reduced to 4.5 tablets/month (reduction by 35.7%, $P = 0.016$). The number of abortive drugs was further reduced in the following 3 months of treatment to 4 tablets/month (reduction by 42.9%, $P = 0.006$). These results were mainly due to a decreased triptan use whereas the intake of other medication, i.e. NSAIDs, was not significantly attenuated.

Migraine attack duration was 50 h at baseline. After 3 months of treatment the duration of attacks was reduced by 22–28 h/attack ($P = 0.098$). After 6 months of treatment the median duration of migraine attacks remained at 28 h.

There was no significant reduction in headache intensity during the treatment with riboflavin. At baseline the headache intensity was 3.3/5. After 3 and 6 months of treatment the headache intensity was not changed (3/5; $P = 0.296$).

During the whole study three patients experienced very mild adverse effects. Adverse effects were diarrhoea, upper abdominal pain and facial erythema.

Discussion

We could demonstrate that prophylactic riboflavin treatment reduced migraine attack frequency and attenuated the use of abortive anti-migraine tablets after 3 and 6 months. Although headache duration decreased from 50 h at baseline to 28 h in the third and sixth month (by 44%) statistical significance was not reached. Riboflavin failed to show an effect on headache intensity.

In line with the placebo-controlled study by Schoenen *et al.* (1998) we could show a significant reduction in headache frequency by using an open labelled study design. In this placebo-controlled study the mean monthly attack frequency was 3.82 in the active group and decreased to a median of 2. A second study investigating the effect of β-blockers and riboflavin treatment on auditory-evoked cortical potentials

demonstrated a reduction from 3.51 attacks/month to 1.7 attacks/month (Sándor *et al*., 2000). Our findings support these data as we could demonstrate a reduction of monthly attack frequency.

The intake of abortive anti-migraine drugs was attenuated by riboflavin, 400 mg/day, in our study because of a reduction of triptan use. The intake of other analgesics was not changed. These findings are in contrast to results from previous trials in which the use of acute anti-migraine drugs was not altered (Schoenen *et al*., 1998).

Triptans as the main abortive drug in migraine pain were significantly less used compared with baseline, whereas the use of OTC analgesics was unchanged. In the study by Schoenen *et al*. the intake of all abortive medications was analysed. We performed an analysis of different groups of abortive agents. This may explain the fact that in our study we could demonstrate a significantly reduced intake of triptans. If we have looked for all abortive agents, our results would not have reached statistical significance.

Riboflavin exerts the adverse events with three side-effects in 23 patients in our study compared with a similarly low number of adverse events in the literature in previous trials with 28 subjects in the *verum* group (Schoenen *et al*., 2000). In this initial study one patient withdrew from the study because of gastric intolerances that most likely were caused by the additional treatment with 75 mg aspirin. In a comparative trial studying the efficacy of aspirin versus metoprolol as prophylactic agents in migraine 31.1% in the aspirin group and 39.3% in the metoprolol group experienced adverse events (Diener *et al*., 2001). There is no evidence that riboflavin interacts with abortive medication, as do many other prophylactic agents (Ferrari *et al*., 2003).

Schoenen *et al*. (1998) demonstrated a significant reduction of migraine days. We could observe a clear trend indicating a reduction of monthly headache hours by 44% after riboflavin treatment. However, our study did not reach statistical significance. Whilst headache hours were reduced the headache intensity did not change in this study. This finding is in accordance with previous studies (Schoenen *et al*., 1998).

The results of our study should be interpreted carefully. First, the sample size was only 23 patients and therefore smaller than in previous trials with 48 patients in the open pilot study and 54 in the placebo-controlled study. The small sample size may have accounted for the failure to show a reduction in headache hours. However, most of our results are in line with data from the literature.

We did not choose a placebo-controlled design because our patients are recruited from a tertiary care centre and most patients have been treated previously with multiple other prophylactic agents. From 23 patients in our study five patients had treatment failures with one preventive treatment and 12 patients had >2 treatment failures with prophylactic agents. However, despite the shortcomings of our study we could demonstrate an effect of riboflavin in this patient group. We propose a second randomized, placebo-controlled study with a larger number of patients to validate the findings of the previous studies. An experimental animal study by França *et al*. (2001) could demonstrate a dose-dependent analgesic effect of riboflavin. There, a dose-defining study should be performed for the prophylactic treatment of migraine.

In summary, we could show the efficacy of riboflavin in an outpatient clinic for tertiary care. In line with previous studies, we propose riboflavin as an alternative choice for prophylactic anti-migraine treatment.

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