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Research Submission

A Randomized Double-Blind Placebo-Controlled Trial of Thioctic Acid in Migraine Prophylaxis

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Background.—Impaired mitochondrial phosphorylation potential may play a role in migraine pathogenesis. Metabolic enhancers, such as riboflavin or coenzyme Q, are effective in migraine prophylaxis and quasi-devoid of adverse effects. Thioctic acid (-lipoïc acid) is another substance known to enhance energy metabolism in mitochondria and to be beneficial in diabetic neuropathy.

Objective.—After an open pilot study suggesting its therapeutic antimigraine potentials, we embarked therefore in a randomized controlled trial of thioctic acid (Thioctacid) in migraine prophylaxis steered by the Belgian Headache Society.

Methods.—Five Belgian centers recruited 54 migraineurs (43 migraine without aura, 11 with aura; mean age 38 $\pm$ 8 years; 7 males). After a 1-month single-blinded run-in period, 44 patients received either placebo (n = 18) or thioctic acid 600 mg p.o./day (n = 26) for 3 months.

Results.—Statistical analysis was carried out on an intention-to-treat basis. Monthly attack frequency tended to be reduced between run-in and the 3rd month of treatment in the thioctic acid group compared to placebo (P = .06). The proportion of 50% responders was not significantly different between thioctic acid (30.8%) and placebo (27.8%). Within-group analyses showed a significant reduction of attack frequency (P = .005), headache days (P = .009), and headache severity (P = .03) in patients treated with thioctic acid for 3 months, while these outcome measures remained unchanged in the placebo group. No adverse effects were reported. For logistical reasons this trial was interrupted before the planned 80 patients were enrolled.

Conclusion.—Albeit underpowered, this study tends to indicate that thioctic acid may be beneficial in migraine prophylaxis. Before any firm conclusion can be drawn, however, a large multicenter trial is necessary.

Key words: migraine prophylaxis, mitochondria, energy metabolism, thioctic acid

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The exact pathogenesis of migraine is not determined and may be polymorphic. Phosphorus 31 brain nuclear magnetic resonance (NMR) spectroscopy studies have shown that mitochondrial phosphorylation potential is reduced in migraineurs between attacks.[1-3] A deficient energy metabolism could be the missing link between the biobehavioral model and the hypoxia theory of migraine.[4] The "hypoxia" theory of migraine pathogenesis postulates that an imbalance between oxygen demands and availability might be responsible for triggering migraine attacks.[5] The biobehavioral model of migraine hypothesizes that an abnormal response to certain stressors (eg, because of dysfunctioning monoaminergic modulatory systems) is able to activate the frontal cortex and from there other cortical areas and brain stem centers leading to the migraine attack.[6] The latter model offers no satisfactory explanation for an activation of the pain-signaling trigeminovascular system, the former no cause for "hypoxia." An impaired neuronal energy metabolism might thus be the missing link between the 2 theories,[4] as it would explain why an excessive activation of cortical structures could lead to trigeminovascular activation via a metabolic disequilibrium, and possibly via hypoxia-sensing neurons and the hypoxia-inducible factor.

In various mitochondrial cytopathies treatment with so-called metabolic enhancers like high-dose riboflavin (vitamin B2), nicotinamide or coenzyme Q, are able to improve clinical and biochemical abnormalities.[7] Based on these findings, we showed that riboflavin 400 mg per day was effective in migraine prophylaxis in an open pilot study[4] and in a randomized placebo-controlled trial,[8] a finding confirmed by Boehnke et al in a large open study.[9] Along the same line, we also confirmed in a randomized trial that coenzyme Q10, which was suggested to be beneficial for migraineurs in a pilot study,[10] was significantly better than placebo for preventing migraine attacks.[11]

Thioctic acid (α-lipoïc acid—THIOCTACID®, Asta Medica, Germany) is another drug enhancing mitochondrial oxygen metabolism and ATP production.[12] It produced a clinical and biochemical improvement in various mitochondriopathies such as Leigh's encephalomyelopathy,[13-15] pyruvate dehydrogenase deficiency,[16] and pyruvate carboxylase deficiency.[17] Barbiroli et al[1] have shown that thioctic acid increases brain energy availability and skeletal muscle performance as assessed by in vivo 31P-NMR spectroscopy in a patient with mitochondrial cytopathy. Like riboflavin and coenzyme Q10, thioctic acid has few, if any, adverse effects.

Considering these data we performed an open pilot study of 600 mg thioctic acid (Thioctacid®) in 15 migraine patients and found that the drug had a prophylactic effect in 10 out of 13 evaluable patients. In several patients Thioctacid® had a better effect than the previously used prophylactic agent, ie, sodium valproate (5 patients), riboflavin (3 patients), or cyclandelate (1 patient). Only 1 patient complained of gastric side effects but completed the trial. We thought that these results were encouraging enough to embark in a randomized placebo-controlled trial.

PATIENTS AND METHODS

Patients.—The study was conducted in 5 Belgian headache centers. Fifty-four patients were recruited. Their mean age was 38 $\pm$ 18 years and the sex ratio 47 females for 7 males. There were 43 migraineurs without aura and 11 with aura, fulfilling the diagnostic criteria of the International Classification of Headache Disorders 2nd edition (codes 1.1 & 1.2).[18] The patients had 2-6 attacks per month and not more than 10 days of interval headaches per month, which they were able to distinguish from migraine attacks. We excluded from the trial patients with medication overuse, prophylactic antimigraine treatment during the last month, or any other serious medical condition. Women were required to have an adequate contraception. Written informed consent was obtained. The study was conducted in accordance with the Helsinki Declaration and approved by the Ethics Committee of the Faculty of Medicine (Liège University).

Study Design.—The design of this study followed the guidelines of the IHS Committee on Clinical Trials in Migraine.[19] This was a double-blind, parallel group trial of thioctic acid 600 mg or placebo once-daily in a 3:2 randomization protocol. At the first visit, eligible patients received placebo for a 1-month single-blinded run-in baseline phase, after which they were included in the randomized phase if they had presented at least 1 migraine attack. Forty-four of the 54 recruited patients

achieved this selection criterion and were randomly allocated to receive either placebo (n = 18) or thioctic acid 600 mg p.o. during breakfast (N = 26) for 3 months; 4 patients dropped out before visit 2 and 6 patients did not present an attack during the run-in phase.

Patients were provided a diary in which they had to record headache occurrence, duration, and severity on a 3-point scale (3, severe; 2, moderate; 1, mild), presence of nausea and vomiting, of photophobia or visual aura, and number of acute headache medications taken per day. Diaries were cross-checked by the investigators (JS, JJ, PL) and the patient at each monthly visit where compliance was assessed by counting the returned capsules. This investigator-initiated study was sponsored by the Belgian Headache Society. The trial medication and placebo were provided by Asta Medica.

Outcome Measures.—The primary outcome measures were change in monthly attack frequency between the 1st run-in month and the 3rd month of the randomized period, and the same change between run-in and the average of the 3 randomized months. We considered as responders those patients who had at least a 50% reduction of monthly attack frequency between run-in and average of the 3 randomized months. Secondary efficacy measures were number of days with migraine headaches, mean severity and duration of attacks, number of days with nausea or vomiting, and mean number of acute antimigraine tablets taken per migraine day.

Statistics and Data Analyses.—Sample size calculations were based on the difference of 37% observed between placebo and the active drug in the 400-mg riboflavin trial and assumption of a 20% placebo responder rate. To detect a significant difference between the 2 treatments (5% 2-sided significance level) with a 90% power the minimum size of each treatment group was estimated at 44 patients.[20] Because of slow and delayed enrollment in certain centers, only 54 patients could be recruited within 18 months after which the study had to be interrupted because the time limit for quality guarantee of the trial medication was reached.

Statistical analysis (Statistica, StatSoft Inc. v. 6.1, Tulsa, OK, USA) was carried out on an intention-to-treat basis. In the patients' diaries, migraine headaches

Table.—Results and Demographics (Mean ± Standard Deviation)

	Placebo (n = 18)	Thioctic Acid (n = 26)
Age (years)	38.94 ± 8.05	37.46 ± 13.43
Sex ratio	16 F/2 M	22 F/4 M
Diagnosis	9 MO/3MO + MA/6 MA	14 MO/7 MO + MA/5 MA
Migraine history (year)	16.94 ± 10.35	17.75 ± 20.29
Nb attacks/month run-in phase	3.06 ± 1.55	3.46 ± 1.94
Nb attacks/month the 3rd month	3.06 ± 1.55	2.42 ± 1.92
Nb attacks/month average 3 months	3.06 ± 1.58	2.69 ± 1.67
Nb headache days/month run-in phase	5.22 ± 2.46	4.96 ± 3.18
Nb headache days/month the 3rd month	4.61 ± 2.06	3.69 ± 3.92
Nb headache days/month average 3 months	4.55 ± 2.29	3.99 ± 3.57
Severity/attack run-in phase	1.88 ± 0.39	1.99 ± 0.52
Severity/attack the 3rd month	1.82 ± 0.41	1.68 ± 0.80
Severity/attack average 3 months	1.83 ± 0.49	1.69 ± 0.71
Nausea/vomiting run-in phase	1.95 ± 2.29	2.32 ± 1.80
Nausea/vomiting the 3rd month	1.89 ± 1.90	2.38 ± 3.62
Nausea/vomiting average 3 months	1.98 ± 1.87	2.36 ± 3.31
Nb acute medication/attack run-in phase	1.29 ± 1.11	1.68 ± 0.81
Nb acute medication/attack the 3rd month	1.37 ± 0.88	1.72 ± 1.24
Nb acute medication/attack 3 months	1.42 ± 0.98	1.61 ± 0.96
Headache duration/attack run-in phase (hours)	9.69 ± 5.47	7.70 ± 6.58
Headache duration/attack after 3rd month (hours)	9.30 ± 4.61	7.08 ± 6.43
Headache duration/attack average 3 months (hours)	8.78 ± 3.58	6.54 ± 5.91

MO = migraineurs without aura; MA = migraineurs with aura.

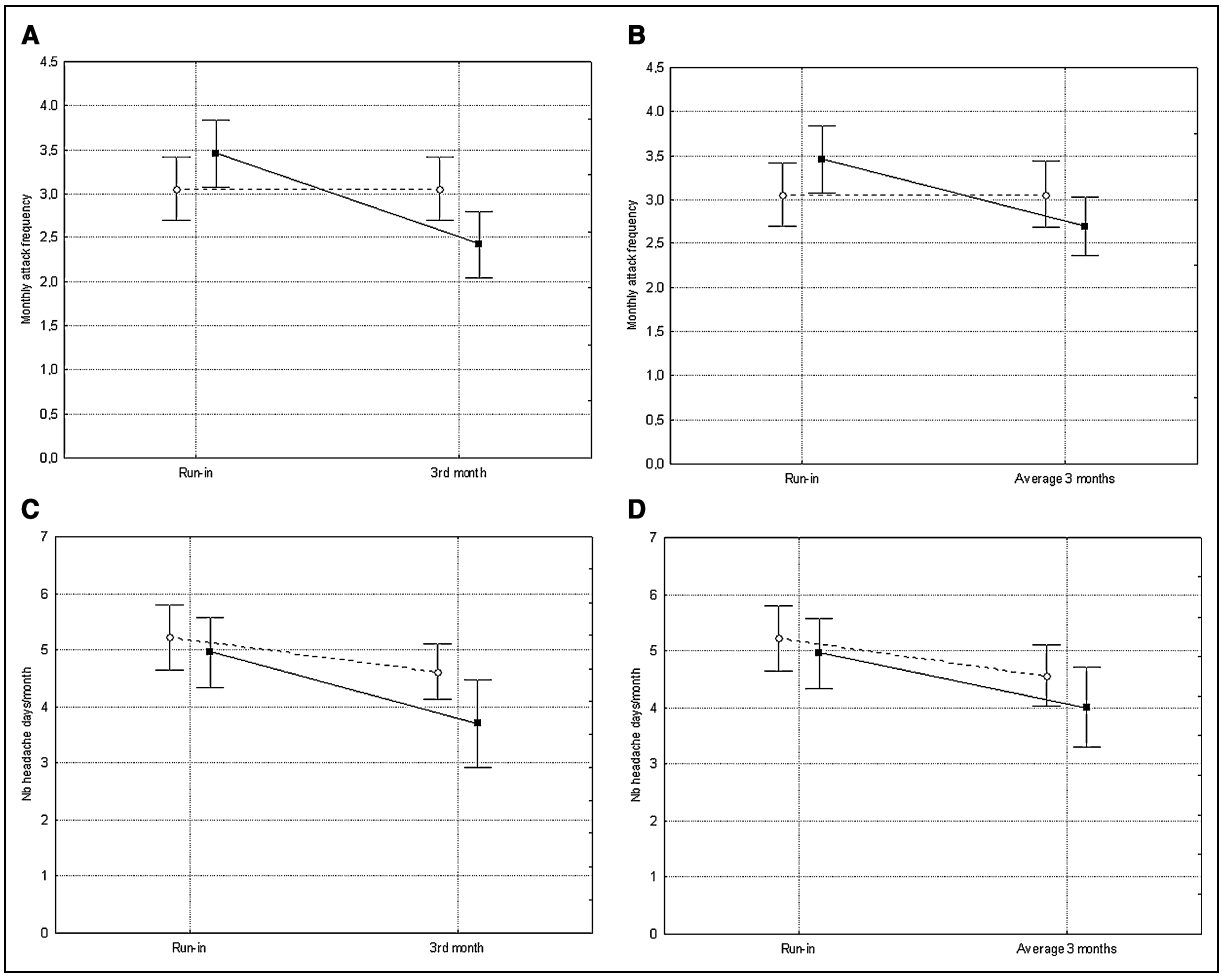

Fig 1.—Mean monthly number of attacks (A, B) and headache days (C, D) during the run-in phase compared to the 3rd month (A, C) and the averaged 3 months of randomization (B, D) in thioctic acid (filled squares, continuous line) and placebo groups (open circles, dashed line). Vertical gratings represent standard errors.

separated by less than 24 hours were counted as 1 single attack. Seven patients dropped out after 2 months in the randomized phase (for lack of efficacy [3], interruption of contraception [1] and unknown reason [3]). Data for these patients were included in the analysis according to the last value-carried-forward method. Analysis of variance (ANOVA) was used for comparison of primary and secondary outcome variables between the 2 treatment groups, χ^2 for demographic and nosographic data, Fisher's 2-tailed exact test for responder rate, and the univaried planned comparisons sign test for changes between baseline and the second, third, or 4th month of treatment within placebo and thioctic acid groups. All statistical analyses were 2-tailed. *P* values less than .05 were considered as significant.

RESULTS

The results and demographics are summarized in the Table. The 2 treatment groups did not differ significantly by mean age, migraine type, or duration of disease, nor did they by baseline migraine frequency.

Treatment Efficacy.—Monthly attack frequency between run-in and the 3rd month of randomization tended to be reduced after thioctic acid compared to placebo, but the difference just fell short of statistical significance ($P = .06$) (Fig. 1A). There was also a trend for an attack frequency reduction between the run-in month and the averaged 3 months of randomization in the thioctic acid group but not placebo arm ($P = .09$) (Fig. 1B).

The proportion of responders, ie, patients with $\geq$50% reduction in monthly attack frequency

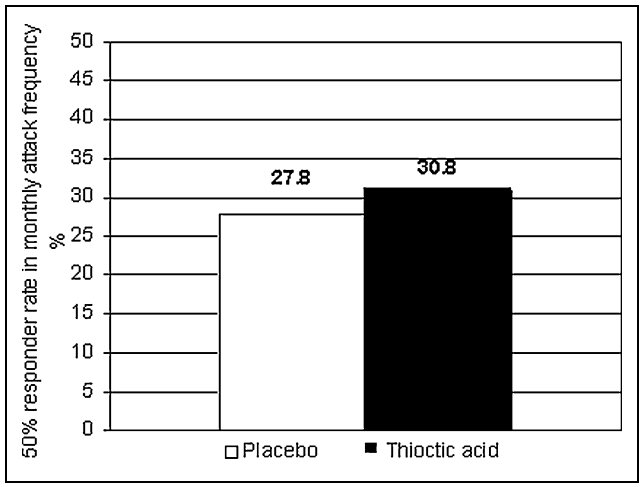

Fig 2.—Fifty percent responder-rate in monthly attack frequency at the end of the 3rd month of treatment with placebo (white) or thioctic acid 600 mg per day (black).

(Fig. 2) was not significantly different between thioctic acid and placebo: for baseline—3rd month comparison 27.8% after placebo and 30.8% after verum ($P = .83$); for baseline-averaged randomization period comparison 16.7% after placebo and 19.2% after verum ($P = .83$).

As far as secondary efficacy measures are concerned, the changes that occurred in number of headache days (Fig. 1C,D), headache severity, days with nausea or vomiting, number of acute headache medication or headache duration between the placebo run-in phase and the randomized period were not significantly different between the thioctic acid and placebo arms neither for the 3rd month assessment nor for the results averaged over the 3 months of randomization (Table).

Within-group analyses showed significant changes in primary and some secondary outcome variables in patients treated with thioctic acid but not in those who received the placebo. Reductions between the run-in phase and the 3rd month of Thioctacid® and run-in and averaged results over the 3 months of Thioctacid® treatment, respectively, were significant for attack frequency ($P = .005/.01$), headache days ($P = .009/.02$), and headache severity ($P = .03/.03$).

Adverse Events.—No side effects were reported. Seven patients dropped out during the 3rd month of the randomized phase, 2 in the placebo, 5 in the verum arm. Five were lost to follow-up; 2 patients, 1 in each treatment arm, withdrew from the study because of lack of improvement. There were no significant changes in weight during the trial period ($P = .5$).

COMMENTS

As far as the predefined primary outcome measures are concerned, this RCT shows a clear trend for reduced migraine frequency after 3 months of prophylactic treatment with thioctic acid compared to placebo, but no significant result. On within-group analysis there is a significant effect on attack frequency, headache days, and severity for thioctic acid, but not of placebo.

These equivocal results can probably be explained by the fact that the study was underpowered. Recruitment had indeed to be interrupted before the planned number of 80 patients was reached because the time limit for quality guarantee by the producer Asta Medica was exceeded. The study illustrates the difficulties certain centers encounter recruiting patients for a nonsponsored drug trial.

The statistical trend for a superior reduction of attack frequency by thioctic acid than by placebo was more pronounced for the comparison between run-in phase and 3rd month of treatment ($P = .06$) than for the one between run-in and the averaged 3 months of randomization ($P = .09$). This suggests that the effect of thioctic acid accrues over time and that maximum efficacy is not reached before several months of treatment, like in the riboflavin[8] and coenzyme Q10[11] studies. Intuitively, one may indeed expect that a treatment targeting a metabolic dysfunction may take longer before becoming efficient than one that acts on neurotransmitters or neuronal excitability.

Tolerance of thioctic acid was excellent. There were no known drop-outs because of adverse effects and no weight gain. From this perspective, thioctic acid is in line with the other metabolic enhancers used in migraine which have over classical antimigraine prophylactics the advantage to be much better tolerated.

To conclude, this trial provides no proof for the efficacy of thioctic acid 600 mg per day in migraine prophylaxis. It nonetheless tends to confirm that this

drug has an interesting therapeutical potential in migraine and that its tolerance is excellent, suggesting that larger and longer randomized controlled trials are worthwhile.

Conflict of Interest: None

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