HIGH LIGHT

Efficacy of coenzyme Q10 in migraine prophylaxis: A randomized controlled trial

Abstract—Riboflavin, which improves energy metabolism similarly to coenzyme Q10 (CoQ10), is effective in migraine prophylaxis. We compared CoQ10 (3 × 100 mg/day) and placebo in 42 migraine patients in a double-blind, randomized, placebo-controlled trial. CoQ10 was superior to placebo for attack-frequency, headache-days and days-with-nausea in the third treatment month and well tolerated; 50%-responder-rate for attack frequency was 14.4% for placebo and 47.6% for CoQ10 (number-needed-to-treat: 3). CoQ10 is efficacious and well tolerated.

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Mitochondrial dysfunction resulting in impaired oxygen metabolism may play a role in migraine pathogenesis.[1,2] Riboflavin (Vitamin B2) and coenzyme Q10, both known to improve abnormalities in mitochondrial encephalomyopathies[3,4] have been studied in migraine prophylaxis, riboflavin in a randomized controlled trial,[5] and CoQ10 (150 mg/day) in an open-label investigation.[6]

Methods. Patients were recruited during 2002 (trial completion March, 2003). Patients (18–65 years) were eligible if they met International Headache Society (IHS) criteria for migraine with/without aura[7] with a migraine history ≥1 year, two to eight attacks per month, ≤5 days/month of interval headaches, no over consumption of acute anti-migraine medication, no other prophylactic medication (washout ≥3 months), no serious organic or psychiatric disease; only women with contraceptive protection. Written informed consent was obtained. The process of patients through the trial phases follows the CONSORT flow chart.

CoQ10 and placebo were provided by MSE Pharmazeutika GmbH, Germany. A liquid formulation of water dispersed nanoparticles comprising a supercooled melt of CoQ10 with modified physicochemical properties (MSE 2001, guttaQuinon; US-patent 6.197.349) was used.

Placebo consisted of the same ingredients as verum-instead CoQ10, they contained Quinolin yellow (E 104) and Ponceau red (E 124), classified as fit for human consumption in the European Union (EU) and Switzerland and without any known effect on migraine.

The design of this double-blind, randomized, two-parallel group trial followed the IHS Committee on Clinical Trials in Migraine guidelines,[8] current EU guidelines on Good Clinical Practice, and the Declaration of Helsinki. It was approved by the Ethics Committees of both, Canton Zurich and the Medical Faculty, Liège University.

At the first visit, patients received placebo for a 1-month baseline. At the second visit, they were randomized to CoQ10 or placebo if they had presented at least one migraine attack. Medications were randomized in blocks of 10 packages (five placebo, five CoQ10) with a different order for each block, known only to MSE. Each investigator received three blocks containing medication for 10 patients, each. Medication was delivered in 100 ml bottles (with dropper, labeled with patient number and month of treatment), and handed out at each consultation. Patients were allocated in sequence to the randomized phase. Sealed envelopes with treatment codes were added; only the code of one patient with cutaneous allergy was broken.

Dosage was three times daily, 100 mg CoQ10 (or placebo), corresponding to 2 ml (44 drops) of the solution. Patients used a migraine diary (headache severity, nausea/vomiting, name/number of acute headache medication, headache duration). Attacks separated by ≤24 hours were counted as one.

Primary outcome variable was change of attack frequency in month 4 compared with baseline. Secondary outcome variables were reduction of migraine days, mean duration/day, mean severity/day, days with nausea/vomiting, and mean number of units of acute anti-migraine medication/migraine day.

Responders for attack frequency (≥50% reduction) were calculated and the number-needed-to-treat (NNT) determined. Patients were interviewed about adverse events at each visit.

Sample size calculations were based on the trial on riboflavin.[5] Statistical analysis was done on an intention-to-treat population applying the last visit carried forward method. Mann–Whitney U test was used for differences between groups, χ^2 test for 2 × 2 contingency tables of responder rate, general linear mixed model for evolution over time. Significance level was $p = 0.05$, after accounting for multiple comparisons. SAS (Windows 8.02) was used.

Results. Among the patients presenting (numbers not recorded), 50 were recruited. Seven patients interrupted the study after the baseline month (before randomization): four were lost to follow-up, two were not entered for lack of compliance, one withdrew because of intermittent pyrosis. Forty-three patients were randomized to placebo (n = 21) or CoQ10 3 × 100 mg/day (n = 22). Six patients dropped out after randomization: three for lack of efficacy (two with placebo), two were lost to follow-up in the verum group after the second month. One patient in the verum group withdrew because of cutaneous allergy after having started the treatment and was therefore not included into statistical analysis. Apart from headache duration, which was larger in verum (20 ± 13 years vs 14 ± 8 years, $p = 0.032$), groups were comparable (table 1).

The primary outcome variable, the change from baseline to month 4 (third treatment month) in attack fre-

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The study was supported by MSE Pharmazeutika GmbH, D-61352 Bad Homburg, Germany (www.mse-pharma.de); the use of CoQ10 in pain, including migraine, is patent pending in the United States and Europe. Dr. Schoenen has received honoraria from the sponsor of the study.

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Table 1 *Characteristics of patients at baseline*

	Placebo (n = 21)	CoQ10 (n = 21)	*p* Value
Age, y	39.6 ± 16	37.7 ± 12	0.66
No. of women	16 (76.2%)	18 (85.7%)	0.70
No. of migraineurs with aura	1 (4.8%)	1 (4.8%)	>0.99
Headache duration, y*	14 ± 8	20 ± 13	0.032
Attack frequency, no. of attacks/mo	4.4 ± 1.6	4.4 ± 1.9	>0.99
No. of headache days/mo	7.2 ± 3.0	7.2 ± 4.6	>0.99
Mean duration of migraine/day, h	6.0 ± 3.4	7.6 ± 4.8	0.23
Mean attack severity (4-point scale)	1.6 ± 0.6	1.7 ± 0.5	0.78
No. of days with nausea	1.9 ± 2.2	2.0 ± 2.8	0.95
Mean no. of tablets/day	1.3 ± 0.7	1.1 ± 0.6	0.26

* Log-rank test.

Values are in mean ± SD.

CoQ10 = coenzyme Q10.

quency, was more pronounced in the CoQ10 group compared to placebo ($p = 0.05$, table 2) with a difference in attack frequency ($p = 0.01$) and a continuous decrease in attack frequency between month 1 and 4 ($p = 0.03$) only in the CoQ10 group (figure).

The 50%-responder-rate for headache frequency was higher in CoQ10 than in placebo. The distribution of patients according to the change in attack frequency between month 4 and baseline was different between CoQ10 and placebo. While in the placebo group, the distribution was scattered around "no change" (five patients) with both, increase and decrease in attack frequency in eight patients each, in the CoQ10 group it was bimodal with 15 patients decreasing in attack frequency, one patient without any change and five with an increase.

Table 2 *Outcome variables*

	Placebo (n = 21)	Verum (n = 21)	*p* Value*
No. of migraine attacks/mo	−0.09 ± 1.9	−1.19 ± 1.9	0.05
No. of days with headache/mo	−1.4 ± 3.6	−1.9 ± 3.9	0.80
Mean severity of migraine/day	0.3 ± 1.04	−0.4 ± 1.2	0.25
No. of days with nausea/vomiting	0.8 ± 2.2	−0.9 ± 1.8	0.02
Mean no. tablets/day	−0.02 ± 0.5	0.004 ± 0.9	0.71
Mean duration of migraine/day	−0.5 ± 4.1	−2.6 ± 5.9	0.11
50% Responder rate for attack frequency	3 (14.3%)	10 (47.6%)	0.02

* Mann-Whitney *U* test; χ^2 test for responder rate.

Change from baseline (month 1) to month 4. Values are means ± SD.

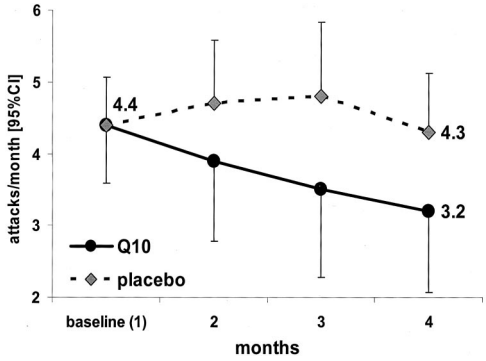

*Figure. Mean number of migraine attacks per month during the 4-month trial in placebo (n = 21; [gray triangles], dashed line) and coenzyme Q10 (CoQ10) 300-mg groups (n = 21; [black circles], continuous line). The change from third treatment month to placebo baseline was significant for CoQ10 (*p *= 0.01), but not for placebo (*p *= 0.81).*

The number of headache days was different between month 4 and 1 ($p = 0.04$) in the CoQ10 group only.

The change between baseline and month 4 in the number of days with nausea was different between the groups ($p = 0.02$), with a different evolution ($p = 0.039$). Also, the evolution of mean severity differed between groups ($p = 0.013$).

For severity, mean duration, and acute medication use, groups did not differ, neither did the treatment results across centers. No change of outcome variables was detected in placebo (comparison month 4/baseline; evolution over time). The NNT for 50%-responder-rate (attack frequency) was 3. During the placebo-baseline, one patient withdrew because of intermittent pyrosis. In the CoQ10 group, one patient withdrew because of cutaneous allergy.

Discussion. This randomized controlled trial confirms the results of a previous open label study.[6] The low proportion of migraine with aura patients was coincidental. The effect of CoQ10 seems to begin after the first month and to be maximal after 3 months. It is most pronounced on attack frequency and gastrointestinal symptoms and weaker for the number of headache days and headache severity. For headache duration and acute anti-migraine drug consumption, nonsignificant trends in favor of CoQ10 were observed.

A lag before significant improvement over placebo has been observed, similarly to riboflavin.[5] It is conceivable that a clinical effect due to improved mitochondrial function might build up more slowly than one mediated by receptor blockade (e.g., beta blockers).

Average reduction in attack frequency was lower in the present placebo-controlled trial compared to the open study.[6]

Therapeutic gain of CoQ10 over placebo for 50%-

responder-rate in attack frequency was 33%, and similar to riboflavin (37%).[5] Tolerability was excellent, with one adverse effect in the verum group, a cutaneous allergy.

The placebo response of 14% is small, but similar compared to the trial on riboflavin,[5] where it was 19%. Using placebo during the first baseline month, as we did in accordance with IHS guidelines,[8] prevents the randomization of some placebo responders, which in our study was up to 10% (four individuals) of the recruited patients. Furthermore, placebo response includes expectations and beliefs.[9] CoQ10 is sold as a dietary supplement, which might lead to low patient expectations concerning efficacy and be associated with a low placebo response.

The dose of 300 mg of CoQ10 was chosen because comparable doses were previously used to treat neurologic disorders.[10] The different dosage from the open trial[6] is explained by the independent planning of the studies. For clinical practice, lacking information on optimal dosing and formulation, starting high and diminishing gradually seems to be reasonable.

Because of its excellent tolerability, CoQ10 is a candidate for children or women of childbearing age. Further studies are needed to examine migraineurs with aura and confirm the role of CoQ10 in migraine prophylaxis.

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