PharmacologyOnLine
April 30, 2013
Archives • 2013 • vol.1 • 39 - 46

Magnesium, L-Tryptophan and Niacin in Prophylaxis Therapy of Pediatric Migraine

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Abstract

The present study evaluates the efficacy and tolerability of magnesium, l-tryptophan and niacin in prophylaxis therapy of pediatric migraine.

For our study, 20 outpatients, (13 F, 7 M) mean age 8.5 years (SD 1.5), range 6-12 years, suffering from migraine without aura (ICDH '04 criteria) were enrolled. The mean duration of disease was 1.8 (SD 0.8) years, range 1-3 years. At baseline the mean frequency of attacks was 7.4/month (SD 2.1), range 4-12; the mean number of drugs intaking for acute attacks was 6.3 tablets/month (SD 1.8). During the six month evaluation period magnesium 45 mg, l-triptophan 175 mg, and niacin 12.5 mg (per os twice daily) was administered . All patients filled a headache-diary card during the evaluation.

The results of our study indicates that the basal frequency of attack was 7,4 (SD 2.1) and 4,4 (SD 1.9), 3,3 (SD 1.8), 2,4 (SD2.2), after 1, 3 and 6 months respectively [P=0.003; P<0.0001; P<0.0001].The basal value of intaking drugs for acute attacks was 6,3 (SD 1.8) and 3,8 (SD 1.6), 2,6 (SD 1.6), 1,8 (SD1.6) after 1, 3 and six months respectively [P=0.0001; P<0.0001; P<0.0001](T-test analysis). Magnesium, l-triptophan and niacin was well tolerated (4 patients complained somnolence, asthenia, lack of concentration and gastralgia but none patient withdrew the study).

These data showed a good efficacy in reduction of frequency and intensity of headache attack, a good tolerability and a very good reduction of drugs intaking for acute attacks. Our study suggests that magnesium, l-triptophan and niacin could be an alternative therapy for pediatric migraine prophylaxis.

Key Words: magnesium, l-triptophan, niacin pediatric migraine

Introduction

Migraine is a neuro-vascular syndrome characterised by recurrent headache attacks associated with photophobia, phonophobia, nausea and vomiting. Migraine occurs in about 18 % of women and 6% of men, regardless of race or geographical location [1]. Currently, migraines are divided into two categories: migraine without aura (previously termed common migraine), and migraine with aura (previously also termed classical migraine) preceeded by a 15-20 minute episode of visual or sensory aura. Auras are most commonly visual alterations, such as hemianopsic field defects and scotomas that enlarge and spread peripherally [2] Visual auras are associated with spreading cortical depression; sensory auras are usually experienced as paraesthesias of the arm and face.

While the exact etiology of migraine headaches is unknown, several theories have been proposed. The vascular theory attributes migraines to an initial intra-cranial arterial vasoconstriction, resulting in reduced blood flow to the visual cortex, followed by a period of extra-cranial vasodilation [3]. Modern imaging techniques have shown that during a common migraine attack there are in fact only minor changes in cerebral blood flow, and the proposed initial vasoconstrictive phase may actually last much longer than the aura [4]. It has also been hypothesised that migraine sufferers have an inherent vasomotor instability and are more susceptible to the vasodilatory effects of certain physical and chemical agents. This point of view has been reinforced by the observation that organic nitrates, which are capable of delivering nitric oxide, trigger migraine attacks in migraineurs, at low doses, ineffective in normal subjects [5] .

Moskowitz's theory involves the trigeminovascular complex, which links the aura and the headache of migraine [6] (Moskowitz, 1984). In this theory the trigeminovascular neurons release substance P and other neuro-transmitters in response to various triggers .

Migraine is a common disorder also in children. Estimates indicate that 3.5-5% of all children will experience recurrent headaches consistent with migraine. As in adults, most children (approximately 60%) have migraine without aura. Approximately 18% have only migraine with aura, 13% have both, and 5% experience only aura [7-9].

Migraines are incapacitating, throbbing headaches frequently located in the temples or frontal head regions. In children, the headaches are often bilateral (frontotemple) and may be nonthrobbing. Aura is infrequent prior to age 8 years. During the migraine episode, the child often looks ill and pale. Nausea and vomiting are frequent, particularly in young children. Patients avoid light (photophobia), noise (phonophobia), strong odors, and movement. Relief typically follows sleep [7-9].

Initial evaluation focuses on excluding other conditions. Management consists of identifying triggering factors, providing pain relief, and considering prophylaxis.

Conditions that are relatively common in the pediatric population and are thought to be variations and/or precursors of migraine include the following:

- Benign paroxysmal vertigo
- Cyclic vomiting
- Paroxysmal torticollis
- Transient global amnesia - Rare in children
- Acute confusional migraine

Migraine drug treatment, both in adult and pediatric patients, aims either to blunt the headache attack or to reduce the intensity and the frequency of the attacks (preventive treatments), particularly when they are frequent and characterized by intense pain. Triptans can be considered as the most important drugs for the treatment of the attack; they act on 5-$HT_{1B/D/F}$ receptors located on presynaptic trigeminal nerve endings, and, possibly on vascular smooth muscle and in CNS [10].

Other symptomatic drugs include NSAIDs and ergotamine. Several different drug treatments have been attempted to decrease the intensity and the

frequency of migraine attacks; these include beta-blockers, tricyclics such as amitriptyline, some 5-HT_2 receptor antagonists such as methysergide and pizotifen, calcium antagonists such as flunarizine [11]. Non-conventional treatments, such as acupuncture, have also revealed some efficacy in migraine prevention [12]. In addition to these numerous preventive treatments, some minerals, coenzymes and vitamins, often designed as micro-nutrients rather than drugs, have been shown to be effective in migraine prevention or could be considered as a potential approach.

Therefore, the purpose of the present study is to evaluate the efficacy and tolerability of magnesium, l-tryptophan and niacin in prophylaxis therapy of pediatric migraine.

Patients and Methods

The study was performed and approved by Neurophysiopatology Service, Headache Centre, S. Luca Hospital, Vallo della Lucania (SA),Italy.

We studied 20 pediatric outpatients, (13 F, 7 M) mean age 8.5 years (SD 1.5), range 6-12 years, suffering from migraine without aura (ICDH '04 criteria); the mean duration of disease was 1.8 (SD 0.8) years, range 1-3 years (See Table I). At baseline the mean frequency of attacks was 7.4/month (SD 2.1), range 4-12; the mean number of drugs intaking for acute attacks was 6.3 tablets/month (SD 1.8). During the six month evaluation period magnesium 45 mg, l-triptophan 175 mg and niacin 12.5 mg (per os twice daily) was administered . All patients filled a headache-diary card during the evaluation.

Demographic data, including weight, drugs dosage and duration of treatment, were collected and analyzed. History of pediatric's patients previous migraine treatments and their outcome was analyzed. The frequency of attack/days were evaluated as well as the type, severity, and prevalence of side effects were also evaluated. Another parameter of the valuation was intaking drugs for acute attacks.

We used paired t-test to compare the value of each parameter before the initiation of drugs treatment to the corresponding value at the last follow-up after treatment initiation. The level of significance was set at $p<0.05$.

Results

Table II and Figure 1e 2 report the basal attack frequency/days in pediatric patients before drugs treatment and the basal attack frequency/days in pediatric patients after 1, 2, 3 months drugs treatments and the basal value of intaking drugs for acute attacks and after 1, 2, 3 months drugs treatments. The basal frequency of attack was 7,4 (SD 2.1) and 4,4 (SD 1.9), 3,3 (SD 1.8), 2,4 (SD2.2), after 1, 3 and 6 months respectively [P=0.003; P<0.0001; P<0.0001].The basal value of intaking drugs for acute attacks was 6,3 (SD 1.8) and 3,8 (SD 1.6), 2,6 (SD 1.6), 1,8 (SD1.6) after 1, 3 and six months respectively [P=0.0001; P<0.0001; P<0.0001](T-test analysis). The prophylactic drugs (magnesium 45 mg, l-triptophan 175 mg and niacin 12.5 mg, per os twice daily) were well tolerated: 4 patients complained somnolence, asthenia, lack of concentration and gastralgia but none patient withdrew the study.

Discussion

In this retrospective study of migraine pediatric patients, magnesium, l-typtophan and niacin treatments were able to decrease significantly the attack frequency/days in pediatric migraine without significative side effects thus suggesting that the above drugs could be an alternative therapy for pediatric migraine prophylaxis.

The results of the present study may be supported by previous studies indicating that magnesium, l-tryptophan and niacin could be an alternative therapy for migraine prophylaxis also in pediadric patients.

Regarding the efficacy of magnesium in migraine, in an open trial, more than 3,000 patients with common or classical migraine received magnesium

(usually at a dose of 200 mg/day).52 Almost all of the patients were women and most were of childbearing age [13].

Another uncontrolled study was followed by a double-blind trial in which 20 patients with perimenstrual migraine received 360 mg/day of magnesium or a placebo. The treatments were given for two months, starting on the 15th day of each menstrual cycle and continuing until menstruation. At the end of the treatment period, the "Pain Total Index" (which measures duration and intensity of migraines) was significantly lower in the magnesium group than in the placebo group. The number of days with headaches was significantly reduced in patients receiving magnesium, but not in those given placebo. Prior to the start of treatment, white-blood-cell (WBC) magnesium concentrations were lower in the migraine patients than in healthy controls. [14].

In another double-blind study, 81 patients aged 18 to 65 years with migraines (mean attack frequency, 3.6 per month) were randomly assigned to receive magnesium (600 mg every morning) or a placebo for 12 weeks. 54 The frequency of attacks was significantly reduced in the magnesium group, compared with the placebo group (by 41.6%vs. 15.8%; $p < 0.05$). The duration and intensity of attacks also tended to decrease compared to placebo, but the difference was not statistically significant. Diarrhea occurred in 18.6% and gastric irritation in 4.7% of patients receiving magnesium. One study failed to find a beneficial effect of magnesium for migraine prevention. 55 In that study, 69 patients with migraines were randomly assigned to receive magnesium (242 mg twice daily) or a placebo, in double-blind fashion, for 12 weeks. Response to therapy was assessed according to the criterion of the International Headache Society; i.e. a reduction of at least 50% in the duration or intensity of migraines. Using that criterion, approximately 30% of patients in each group were considered responders, with no significant difference between groups. However, this negative finding should be interpreted cautiously. Only a few studies have measured improvement according to the protocol of the International Headache Society and most of those studies showed no significant benefit from the treatment being tested. Even beta-blockers (a class of drugs known to prevent migraine recurrences) were ineffective when tested by the International Headache Society criteria. [15].

It is noteworthy that 33% of patients receiving magnesium (but only 11% of patients given placebo) felt that their treatment was superior to previously used migraine medications. Thus, the results of this study are not inconsistent with previous reports of a beneficial effect of magnesium. [16].

Magnesium has also been given intravenously to treat acute episodes of migraine.56 Forty patients with an acute migraine attack were given 1 g of magnesium sulfate (in a 10% solution) over five minutes. Fifteen minutes after the infusion, 35 patients (87.5%) experienced at least a 50% reduction in pain. Nine patients (22.5%) had complete relief of pain. In 21 of the 35 patients who improved, relief persisted for 24 hours or more. The effectiveness of magnesium was related to the pretreatment serum concentration of magnesium. This study suggests that intravenous administration of magnesium is an effective treatment for acute migraine attacks, particularly in patients whose serum magnesium concentrations are low. These studies provide a rationale for oral magnesium supplementation for migraine prophylaxis. [17].

A reasonable dosage is 200 to 600 mg/day (the larger amounts should be taken in divided doses with meals to reduce the risk of diarrhea). Intravenous administration of magnesium may also be considered as a method of aborting acute migraine attacks. While measurement of serum ionized magnesium might be useful to predict which patients are most likely to respond to intravenous magnesium, this test is not yet commercially available. [18-19].

Regarding the efficacy of 5-HTP in migraine, in a 6-month trial of 124 people, 5-HTP (600 mg daily) proved equally effective as the standard drug methysergide [20]. The most dramatic benefits seen were a reduction in the intensity and duration of

migraines. Since methysergide has been proven better than placebo for migraine headaches in earlier studies, the study results provide meaningful, although not airtight, evidence that 5-HTP is also effective.

Similarly good results were seen in another comparative study, using a different medication and 5-HTP (at a dose of 400 mg daily) [21].

However, in one study, 5-HTP (up to 300 mg daily) was less effective than the drug propranolol [22]. Other studies that are sometimes quoted as evidence that 5-HTP is effective for migraines actually enrolled adults or children with many different types of headaches (including migraines) [23-25].

One novel, but not really new treatment option, is the administration of niacin (nicotinic acid) through intravenous and/or oral routes. Recently, there have been anecdotal reports demonstrating the effectiveness of niacin for aborting acute migraine attacks [26], and for preventing migraine headaches [27].

In terms of tension-type headaches, it appears that intravenous niacin is of benefit acutely due to its presumed central vasodilatory properties. Like migraines, part of the underlying pathophysiology of chronic tension-type headaches involves central mechanisms, such as the trigeminal system [28]. Chronic tension-type headaches are also associated with cerebrospinal pressure or intracranial venous pressure (or both) [29. In fact, tension-type headaches are more similar to migraine headaches than they are dissimilar, in that they seem to progress into migraine headaches due to an escalating pathophysiological process [30]. Thus, niacin might mitigate the acute phase of tension-type headaches through the same hypothesized mechanism of action described earlier.

Some of the reports did demonstrate prophylactic benefits when niacin was administered orally every day. It is now recognized that a deficit of mitochondrial energy metabolism (i.e., impaired mitochondrial phosphorylation potential) plays a role in the pathogenesis of chronic migraine headaches [31]. Niacin maintains adequate mitochondrial energy metabolism by increasing substrate availability to complex I [32], and this is how it might function as an effective prophylactic agent for migraine prevention. Two other nutritional agents (riboflavin and coenzyme Q10) augment complex I of the mitochondrial respiratory chain, and have been subjected to clinical trials demonstrating their effectiveness for the prevention of migraine headaches [33-35]. A deficit of mitochondrial energy metabolism may play a role in the pathogenesis of migraine. Since niacin improves mitochondrial energy metabolism by increasing substrate availability to complex I, it might also be an effective agent for migraine prevention.

Niacin might also prevent tension-type headaches by improving mitochondrial energy metabolism within the skeletal muscles, and by increasing blood flow and oxygenation to the skeletal muscles. The overall net-effect could be a reduction in lactic acid concentrations, leading to reduced episodes of muscular tension and soreness. Niacin may reduce lactic acid concentrations since supplemental niacinamide (the amide of niacin) has been shown to reduce blood lactate and pyruvate concentrations by more than 50% in a patient with MELAS (mitochondrial encephalopathy, myopathy, lactic acidosis, and stroke-like episodes) syndrome by the third day of treatment [36]. This possible mechanism might only relate to migraine sufferers, however, since plasma levels of lactic and pyruvic acids were found to be significantly higher in migraine patients compared to patients with tension-type headaches and normal controls [36].

In conclusion, the present study indicates that magnesium, l-tryptophan and niacin treatments were able to decrease significantly the attack frequency/days in pediatric migraine without significative side effects thus suggesting that the above drugs could be an alternative therapy for pediatric migraine prophylaxis.

In conclusion, our data showed a good efficacy in reduction of frequency and intensity of headache

attack, a good tolerability and a very good reduction of drugs intaking for acute attacks. Our study suggests that magnesium, l-triptophane, and niacin could be an alternative therapy for pediatric migraine prophylaxis.

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Patients	Sex	Age	Years disease
1	f	7	1
2	f	6	2
3	m	8	2
4	f	9	3
5	m	9	2
6	f	8	1
7	f	10	3
8	m	7	1
9	m	6	1
10	f	8	3
11	m	9	1
12	m	11	1
13	f	12	3
14	f	9	3
15	f	10	2
16	m	8	2
17	f	9	2
18	f	7	1
19	f	9	1
20	f	8	2

Table I: General data of the sample patients

Patients	FA: basal	FA: 1 m	FA: 3 m	FA: 6 m	DI: basal	DI: 1 m	DI: 3 m	DI: 6 m
1	6	5	5	4	6	4	4	3
2	5	3	2	1	4	2	4	1
3	4	3	1	1	4	3	1	0
4	9	5	4	4	6	5	4	2
5	10	3	2	1	7	3	2	0
6	8	4	3	2	6	4	3	1
7	7	2	1	0	7	2	1	0
8	7	3	2	0	5	2	1	0
9	11	5	4	0	6	4	2	0
10	8	8	7	7	6	6	4	4
11	12	10	8	8	10	8	7	5
12	6	6	5	5	5	5	5	5
13	7	4	2	2	3	2	1	1
14	4	3	3	1	3	3	1	1
15	6	4	3	3	6	3	3	3
16	8	5	2	2	7	5	2	2
17	7	5	4	2	8	4	4	2
18	6	5	3	2	7	4	3	2
19	9	3	2	2	9	3	2	2
20	7	2	2	1	6	2	1	0

Table II: Attacks frequency: basal vs follow-up at 1, 3 and 6 months

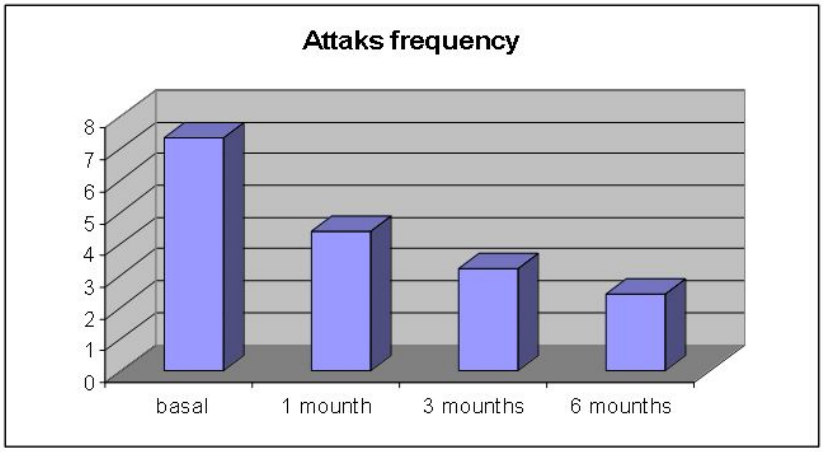

Figure I : Frequency attacks

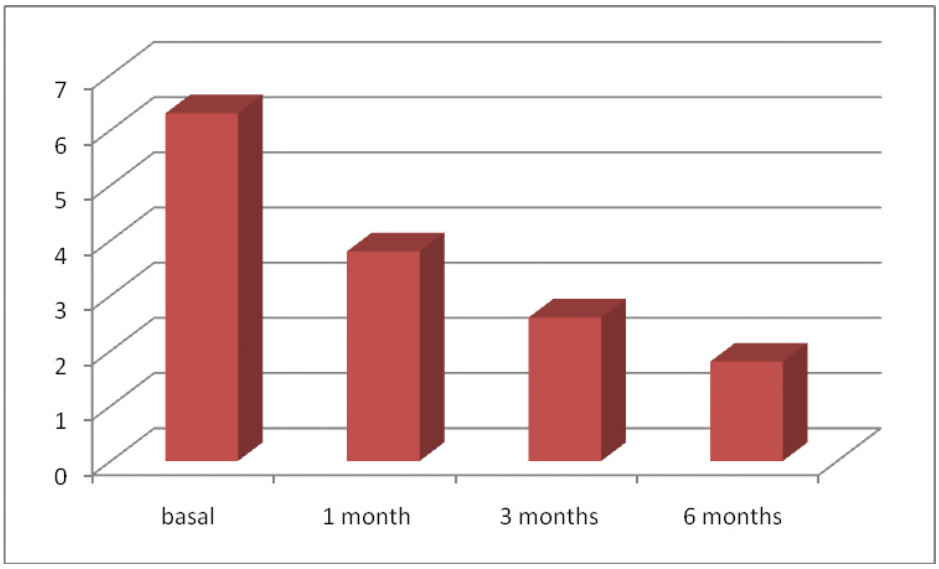

Figure 2: Drugs intake for attacks