



Efficacy and Tolerability of a combination product with L-Tryptophan, *Griffonia simplicifolia*, Vitamin PP and Vitamin B6 in pediatric migraine prophylaxis: an open study

Vincenzo Pizza^{*}, Vincenzo Busillo[°], Domenico Cassano[^], Anella Agresta^{*},
Cesare Colucci d'Amato^{**}, Anna Capasso^{***}

^{*}Neurophysiopatology Unit, Headache Centre, S. Luca Hospital, Vallo della Lucania (SA)

[°]Neurology Division, Headache Centre, Maria SS Addolorata Hospital, Eboli (SA)

[^]Territorial Headache Centre, Distretto N. 60, Nocera Inf. (SA)

^{**}Neurosciences Department, Second University of Naples

^{***}Department of Pharmacy, University of Salerno, Italy

Abstract

The aim of this study was to evaluate the efficacy and tolerability of combination product with L-tryptophan, *Griffonia simplicifolia*, Vitamin PP and Vitamin B6 in prophylaxis therapy of pediatric migraine.

Fifty outpatients (32 F, 18 M), mean age 10.7 years (SD 5.8), range 4-18 years, suffering from ICHD-2 migraine without aura were enrolled. The mean duration of disease was 2.9 (SD 1.6) years, range 1-4 years. At baseline the mean frequency of attacks was 7.6/month (SD 3.3), range 4-12; the mean number of drugs intaking for acute attacks was 6.6 tablets/month (SD 2.2).

During the six month evaluation period the combination product with L-tryptophan, *griffonia simplicifolia*, vitamin PP and vitamin B6 was administered (at dose 100 mg, 480 mg, 18 mg and 1 mg/die, respectively). All patients filled a headache-diary card during the evaluation.

The basal frequency of attack was 7,6 (SD 3.3) and 4,2 (SD 2.6), 3,6 (SD 2.8), 2,2 (SD2.6), after 1, 3 and 6 months respectively [$P < 0.01$; $P < 0.01$; $P < 0.01$]. The basal value of intaking drugs for acute attacks was 7,6 (SD 3.3) and 2,1 (SD 2.5), 1,9 (SD 1.5), 1,4 (SD 2.7) after 1, 3 and 6 months respectively [$P < 0.01$; $P < 0.01$; $P < 0.1$] (T-test analysis). The combination product with L-tryptophan, *griffonia simplicifolia*, vitamin PP and vitamin B6 was well tolerated (11 patients complained somnolence, diarrhea and gastralgia but none patient withdrew the study).

These data showed a good efficacy in reduction of frequency and intensity of headache attacks, a good tolerability and a very good reduction of drugs intaking for acute attacks.

Our study suggests that the combination L-tryptophan, *griffonia simplicifolia*, vitamin PP and vitamin B6 could be an alternative therapy for pediatric migraine prophylaxis.

KEY WORDS: L-TRYPTOPHAN, GRIFFONIA SIMPLICIFOLIA, VITAMIN PP AND VITAMIN B6, MIGRAINE

Introduction

Migraine is a neuro-vascular syndrome characterized 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) preceded 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 hypothesized 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-HT₂ 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 aim of this study was to evaluate the efficacy and tolerability of combination product with L-tryptophan, Griffonia simplicifolia, Vitamin PP and Vitamin B6 in prophylaxis therapy of pediatric migraine.

Methods and Patients

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

We have studied fifty outpatients (32 F, 18 M), mean age 10.7 years (SD 5.8), range 4-18 years, suffering from ICHD-2 migraine without aura were enrolled. The mean duration of disease was 2.9 (SD 1.6) years, range 1-4 years. At baseline the mean frequency of attacks was 7.6/month (SD 3.3), range 4-12; the mean number of drugs intaking for acute attacks was 6.6 tablets/month (SD 2.2).

During the six month evaluation period the combination product with L-tryptophan, griffonia simplicifolia, vitamin PP and vitamin B6 was administered (at dose 100 mg, 480 mg, 18 mg and 1 mg/die, respectively). 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 and Conclusions

The results of our study indicate that the basal frequency of attack was 7,6 (SD 3.3) and 4,2 (SD 2.6), 3,6 (SD 2.8), 2,2 (SD 2.6), after 1, 3 and 6 months respectively [$P < 0.01$; $P < 0.01$; $P < 0.01$]. The basal value of intaking drugs for acute attacks was 7,6 (SD 3.3) and 2,1 (SD 2.5), 1,9 (SD 1.5), 1,4 (SD 2.7) after 1, 3 and 6 months respectively [$P < 0.01$; $P < 0.01$; $P < 0.1$] (T-test analysis). The combination product with L-tryptophan, griffonia simplicifolia, vitamin PP and vitamin B6 was well tolerated (11 patients complained somnolence, diarrhea and gastralgia but none patient withdrew the study).

These data showed a good efficacy in reduction of frequency and intensity of headache attacks, a good tolerability and a very good reduction of drugs intaking for acute attacks.

In this retrospective study of migraine pediatric patients, the combination L-tryptophan, griffonia simplicifolia, vitamin PP and vitamin B6 could be an alternative therapy for pediatric migraine prophylaxis.

The results of the present study may be supported by previous studies indicating that L-tryptophan, griffonia simplicifolia, vitamin PP and vitamin B6 could be an alternative therapy for migraine prophylaxis also in pediatric patients.

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 [13]. 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) [14].

However, in one study, 5-HTP (up to 300 mg daily) was less effective than the drug propranolol [15]. 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) [16-18].

In our study, the beneficial effects of *Griffonia simplicifolia* are because of the amino acid 5-hydroxytryptophan (5-HTP), which is found in the herb's seeds. The compound is extracted from the seeds and taken as a dietary supplement.

In conclusion, our study suggests that the combination L-tryptophan, griffonia simplicifolia, vitamin PP and vitamin B6 could be an alternative therapy for pediatric migraine prophylaxis without significant side effects thus suggesting that the above drugs could be an alternative therapy for pediatric migraine prophylaxis.

Furthermore, 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.

References

- [1] Stewart, W.F., Lipton, R.B., Celentano, D.D. and Reed M.L. (1992) Prevalence of migraine headache in the United States: relation to age, income, race, and other sociodemographic factors. *JAMA* 267, 64-69.
- [2] Greenberg, D. (1993). In "Clinical Neurology". pp. 88-89. Appleton & Lange, Norwalk, CT.
- [3] Hering-Hanit, R., Gadoth, N, Yavetz, A., Gavendo, S. and Sala, B. (2001). Is blood homocysteine elevated in migraine? *Headache* 41: 779-781.
- [3] Wolff, H.G. (1963). *Headache and Other Head Pain*. 2nd Ed. Oxford University Press, New York.
- [4] Campbell, J.K. and Caselli, R.J. (1991) Headache and other craniofacial pain.. In: Bradley WG, Daroff RB, Fenichel GM, Marsden CD, eds. *Neurology in Clinical Practice*, Vol. II, pp. 1525-1526. Butterworth-Heinemann, Boston.
- [5] Thomsen, L.L., Iversen, H.K., Brinck, T.A. and Olesen, J. (1993). Arterial supersensitivity to nitric oxide (nitroglycerin) in migraine sufferers. *Cephalalgia* 13, 395-399.
- [6] Moskowitz, M.A. (1984). The neurobiology of vascular head pain. *Ann. Neurol.* 16, 157-168.
- [7] Bille B et al: Prophylaxis of migraine in children. *Headache* 1977, 17: 61-3
- [8] Adelman JU et al: Migraine prevention medication: a rappresail. *Cephalalgia* 1998, 18: 605-11
- [9] Wasiewski WW: Preventive therapy in pediatric migraine. *J Child Neurol* 2001, 16, 71-8
- [10] Ferrari, M.D., Goadsby, P.J., Roon, K.I. and Lipton, R.B. (2002). Triptans (serotonin, 5-HT_{1B/1D} agonists) in migraine: detailed results and methods of a meta-analysis of 53 trials. *Cephalalgia*. 22, 633-658.
- [11] Diener, H.C., Kaube, H. and Limmroth, V. (1998). Practical guide to the management and prevention of migraine. *Drugs* 56, 811-824.
- [12] Allais, G., De Lorenzo, C., Quirico, P.E., Airola, G., Tolardo, G., Mana, O., and Benedetto, C. (2002). Acupuncture in the prophylactic treatment of migraine without aura: a comparison with flunarizine. *Headache* 42, 855-861.
- [13] De Benedittis G, Massei R. Serotonin precursors in chronic primary headache. A double-blind cross-over study with L-5-Hydroxytryptophan vs. placebo. *J Neurosurg Sci*. 1985;29:239-248.
- [14] Ribeiro CAF. L-5-Hydroxytryptophan in the prophylaxis of chronic tension-type headache: a double-blind, randomized, placebo-controlled study. *Headache*. 2000;40:451-456.
- [15] Ceci F, Cangiano C, Cairella M, et al. The effects of oral 5-hydroxytryptophan administration on feeding behavior in obese adult female subjects. *J Neural Transm*. 1989;76:109-117.
- [16] Cangiano C, Ceci F, Cascino A, et al. Eating behavior and adherence to dietary prescriptions in obese adult subjects treated with 5-hydroxytryptophan. *Am J Clin Nutr*. 1992;56:863-867.
- [17] Cangiano C, Ceci F, Cairella M, et al. Effects of 5-Hydroxytryptophan on eating behavior and adherence to dietary prescriptions in obese adult subjects. *Adv Exp Med Biol*. 1991;294:591-593.
- [18] Cangiano C, Laviano A, Del Ben M, et al. Effects of oral 5-hydroxy-tryptophan on energy intake and macronutrient selection in non-insulin dependent diabetic patients. *Int J Obes Relat Metab Disord*. 1998;22:648-654.

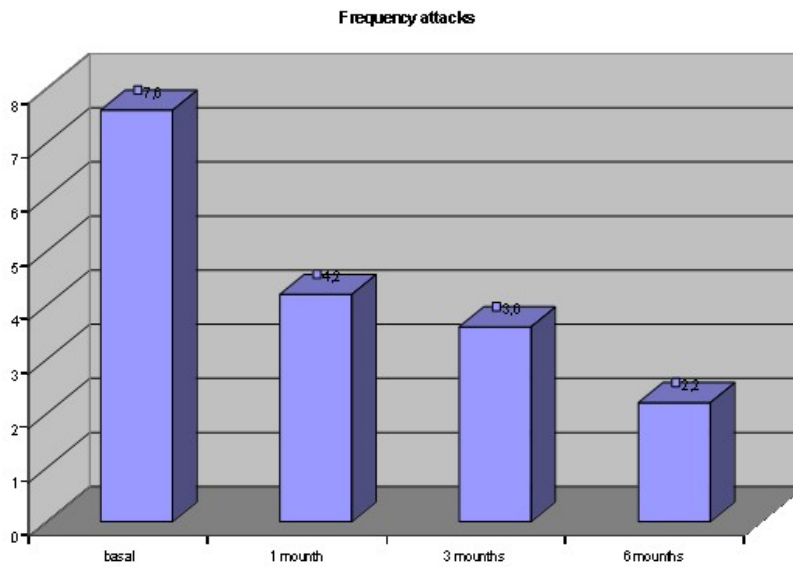


Fig. 1 Frequency attacks (basal vs 1, 3 and 6 months after therapy)

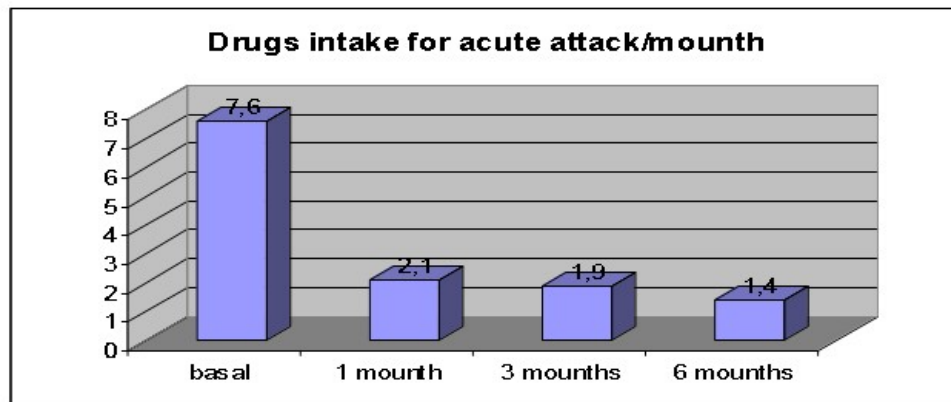


Fig. 2 Drugs intake for acute attack (basal vs 1, 3 and 6 months after therapy)