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# Efficacy of a Combination of *Tanacetum parthenium*, 5-Hydroxy Tryptophan and Magnesium (Aurastop©) in the Prevention of High Frequency Migraine with Aura

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## Abstract

**Object:** To verify the efficacy and safety of the new combination of *Tanacetum parthenium* 150 mg, 5-hydrossitriptophan (5-HTTP) 20 mg and magnesium 185 mg (Aurastop®) in the prophylactic treatment of high frequency migraine with aura (MWA). According to the international headache classification (IHCD 3° beta version) the aura phenomena have a duration of 5 - 60 minutes for any of the usual disturbances (visual, somatosensory and speech disturbance) but no classification describes the frequency of this phenomena. Patients who experience migraine aura emphasize the emotional impact of such a phenomenon, mostly because of the severe, though transient, disability caused by the aura symptoms (*i.e.*, inability to work or driving a vehicle). Furthermore, a profound asthenia lasts for about 48 hours after the resolution of the painful phase. **Materials and Method:** 18 patients (F: n = 10, M: n = 8, mean age: 28) presenting with an ICHD-3 beta diagnosis of migraine with aura (MWA) with a frequency of more than 5 attacks of migraine with aura per month since at least 6 months, were enrolled in the survey and treated with Aurastop© twice a day for a period of 3 months. Diary cards were filled in during a 3-month period before the beginning of the survey and during the 3-month duration of the study. The reduction of MWA attacks per month was assessed as the primary end-point; the reduction of the duration and disability of the aura and of the intensity of the headache were considered as secondary end-points. **Results:** A statistically significant reduction of MWA attacks/month was observed: more than 95% of the patients referred a reduction >50% of the frequency, 66.6% a reduction of more than 70%, and 16.6% a complete disappearance of the attacks after the first week of therapy. More-

over, a sensible reduction of the duration and disability of the aura phenomena was reported by more than 90% of the patients and, in the 55% of the patients also a reduction of the intensity of the headache. No side effects were reported. The efficacy started to appear during the first month of intake and was maintained during the three months of therapy.

## Subject Areas

Neurology

## Keywords

Migraine Aura, Migraine Therapy, Case-Only Study

## 1. Introduction

Migraine ranked as the second most frequent cause of disability worldwide [1]. Epidemiologic studies have consistently indicated that its prevalence is up to 18% in women and 6% in men in Western Countries, with a peak between 22 and 55 years [2]. Among them, about 25% suffer migraine with aura (MWA).

According to the international headache classification (IHCD 3˚ beta version) [3] the aura phenomena have a duration of 5 - 60 minutes for any of the usual disturbances (visual, somatosensory and speech disturbance) but no classification describes the frequency of this phenomena.

Patients who experience migraine aura emphasize the emotional impact of such a phenomenon, mostly because of the severe, though transient, disability caused by the aura symptoms (*i.e.*, inability to work or driving a vehicle). Furthermore, a profound asthenia lasts for about 48 hours after the resolution of the painful phase. This notwithstanding, no aura-specific therapy is available and only sparse studies tried and address this issue so far. Official guidelines from national and international societies indicate lamotrigine (50 - 200 mg daily) as an effective approach to MWA in spite of the relative non-efficacy in the subtype MWoA [4] [5] [6], but the strength of this recommendation is low (III grade). The same is true for many nutraceutical compounds, such as, for example, *Tanacetum parthenium* [7].

According to national and international guidelines, in order to reduce the global impact of migraine, first-line drugs for migraine prophylaxis include beta-blockers, calcium antagonists, anti-depressants, anti-epileptics, onabotulinumtoxinA and phytotherapics plus magnesium [8]. It is generally accepted that a prophylactic treatment should be started in patients who present disabling migraine attacks for at least 4 days per month, and/or in the case of inefficacy of appropriate symptomatic approaches, but no mention is done for the MWA patients.

Recently, several studies have documented the efficacy of the combination of *Tanacetum parthenium*, 5-hydroxy tryptophan and magnesium (Aurastop©) for

migraine treatment and prevention [9] [10] [11] [12].

The antimigraine effect of Aurastop is supposed to be due to the potential effect of its 3 compounds. Parthenolide is an antagonist of TRPA1 and an inhibitor of CGRP release by desensitization and nociceptor defunctionalization.

5-HTP influences the effects of glutamate, a neuropeptide involved in migraine pathogenesis through its excitatory effect on first and second order neurons and its role in the activation of the trigeminovascular system. Moreover, the post-synaptic glutamatergic receptor N-methyl-D-Aspartate (NMDA) is involved on the occurrence of both central sensitization and cortical spreading depression, as demonstrated by its activation during migraine attacks [13] [14] [15]. NMDA receptors are activated by an increase of the synaptic levels of glutamate and inhibited by magnesium. Glutamate levels are regulated by kynurenine which metabolizes l-triptophan in kynurenic acid (KYNA) and quinolinic acid (QUINA). In particular, the NMDA receptor antagonist KYNA inhibits glutamatergic pathway by blocking glutamate release and neurotransmission through its action on the binding site of glycin Glu N1. Recently, it has been observed that in migraineurs the kynuretic pathway is shifted towards the conversion of KYNA in antralinic acid (ANA). This observation is supported by the finding of elevated plasma levels of ANA in migraineurs. Low plasma levels of KYNA may be considered a reliable marker of NMDA receptor activation, while its cerebral levels can be increased by the assumption of its precursor 5-HTP [16]. If assumed as a drug, 5-HTP may, therefore, increase KYNA levels, inhibit peripheral NMDA receptors, and subsequently prevent the activation of the trigeminovascular system and the onset of cortical spreading depression. In addition, TRPA1 and NMDA receptors, glutamate and calcitonin-gene-related peptide (CGRP) are involved in the neurogenic inflammation process, which leads to the sensitization of trigeminal nucleus caudalis in the lower brainstem and upper cervical cord and, consequently, of all the structures implicated in the central transmission of nociceptive information. Molecules that could trigger a migraine attack act as agonist on TRP receptors, leading to a neurogenic inflammation through the release of CGRP from perivascular nerve terminals. Such a cascade might be interrupted by parthenolide, that is, a TRPA1 receptors inhibitor and a powerful inhibitor of nitric oxide (NO) synthase and, consequently, of NO production [17] [18] [19]. Moreover, among its many actions, intracellular magnesium has a physiologic calcium-antagonist effect, resulting in a reduction of the toxic effects of calcium. On the contrary, suboptimal concentrations of this ion favor a free radical accumulation within the cell, which, in turn, may facilitate the onset of a migraine attack [20] [21].

Based on the mechanisms described above, the combination of the three components, *Tanacetum parthenium*, 5-HTP, and magnesium is expected to synergistically influence the biologic pathways involved in migraine pathogenesis, and, therefore, to have a therapeutic potential in migraine prevention.

In the present study we, therefore, aimed at testing the efficacy of Aurastop®

in the prevention of MWA in patients with a high frequency of attacks.

## 2. Material and Methods

From January to December 2017, among all migraine patients referring to the Headache Centre of the Istituto Clinico Città di Brescia, we selected those fulfilling the following criteria: 1) age between 18 and 65 years; 2) diagnosis of MWA, according to the ICHD 3 beta diagnostic criteria; and 3) MWA for at least 6 months with a monthly crisis frequency ranging from 5 to 20 (*high frequency MWA* [HF-MWA]). Psychiatric co-morbidity, other types of acute or chronic pain, kidney failure, neurological or oncologic diseases, and pregnancy were considered as exclusion criteria.

At baseline ($t_0$, screening phase) all patients underwent a thorough neurological examination and were carefully instructed on how to record MWA attacks in their headache diary on a day-to-day basis. In particular, during the observational period of 3 months they were asked to register: 1) number of aura attacks (frequency/month); 2) disability related to the aura (based on a self-rate scale ranging from 0 to 5 where 5 was the maximum disability); 3) duration of the aura (minutes); 4) pain intensity (using the VAS scale, ranging from 1 to 10). At the end of the screening phase, headache diaries were checked, and patients deemed eligible received Aurastop® twice daily for 3 months. During this time, they were invited to continue filling the headache diary. At the end of this further 90-day period ($t_1$) treatment phase, headache diaries were collected and checked exactly as it was done before. In particular, monthly frequency of MWA attacks was considered as the primary endpoint of the study, while duration of the aura, aura-related disability, and pain intensity were considered secondary endpoints. Drug safety was evaluated by treatment discontinuation rate and the occurrence of serious and otherwise adverse events.

### Statistical Analysis

Categorical variables are reported as counts and percentages. Dependent variables were compared by McNemar's $\chi^2$ analysis. Wilcoxon's signed rank test was used to compare migraine characteristics before and after treatment. Statistical analyses were performed using SPSS 21.0 (IBM SPSS Statistics 2013, Armonk, NY, USA).

## 3. Results

Eighteen patients (10 females and 8 males; mean age: 28.5 ± 1.5 years) who suffered HF-MWA were enrolled. All the patients received the treatment under investigation. The results of the analysis are summarized in Table 1 and Figure 1: compared to the 90-day period before Aurastop was administered, we observed a significant reduction of MWA attacks/month during the treatment period. In particular, 17 patients (94.5%) reported more than 50% reduction of MWA attacks, 12 (66.6%) a reduction of more than 70%, and 3 (16.6%) a complete

**Table 1.** Characteristics of aura attacks before ($t_0$) and after ($t_1$) 90-day treatment with Aurastop.

| number | | | duration (minutes) | | | disability (0 to 5) | | | pain intensity (0 to 10) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| $t_0$ | $t_1$ | p value | $t_0$ | $t_1$ | p value | $t_0$ | $t_1$ | p value | $t_0$ | $t_1$ | p value |
| 438 | 48 | <0.001 | 42 ± 1.2 | 18 ± 1.1 | <0.001 | 4 | 1 | <0.001 | 7 ± 1.3 | 4.2 ± 0.9 | <0.001 |

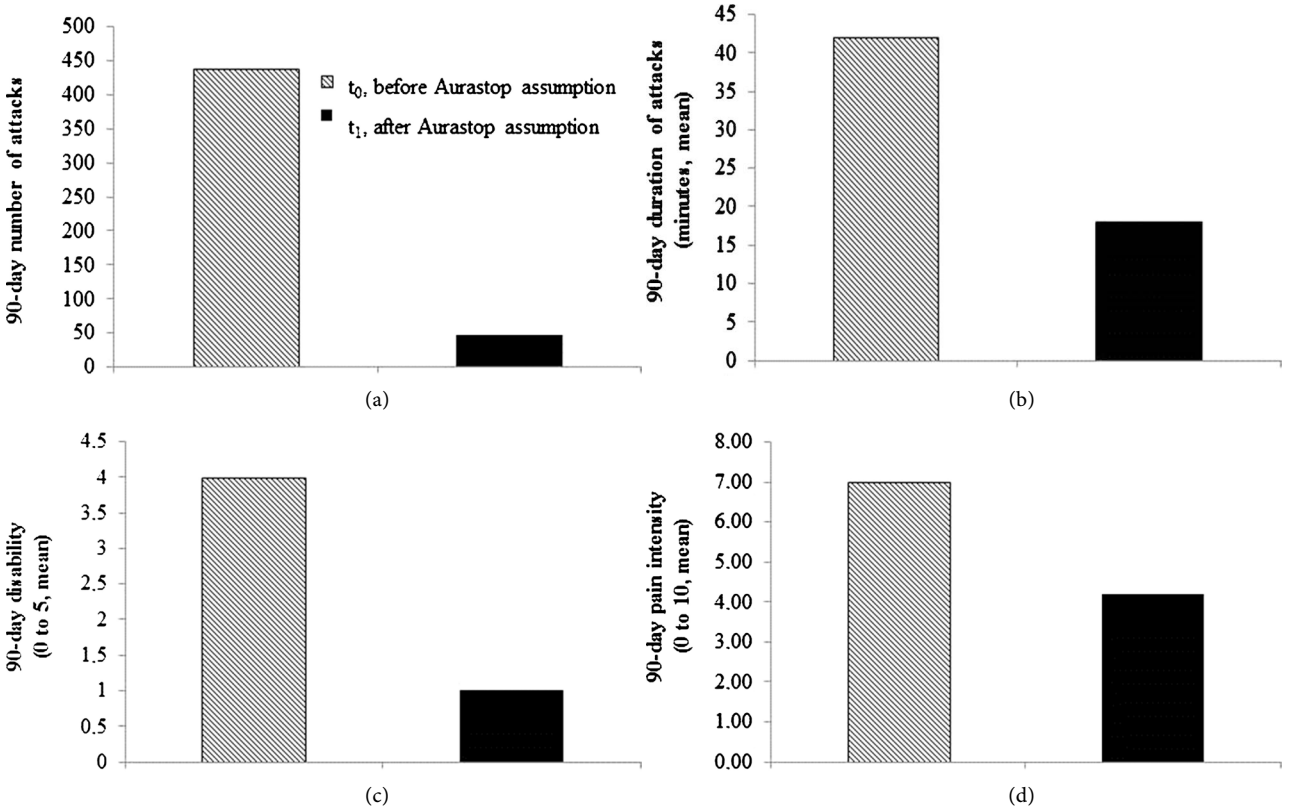


**Figure 1.** Changes in number (a), duration (b), disability (c), and pain intensity (d), by Aurastop assumption ($t_0$ vs $t_1$).

disappearance of the attacks after the first week of therapy. The number of aura attacks, in particular, shifted from 438 in the 3 months ($t_0$) before Aurastop assumption to 48 during the Aurastop intake ($t_1$, $p < 0.001$; **Figure 1(a)**). The benefit conferred by Aurastop was already detectable at the end of the first month of therapy in 15 patients (83.3%) and it was maintained thereafter. A reduction of >50% of aura duration and aura-related disability was reported by 17 patients (94.5%; duration: from 42 ± 1.2 minutes during the $t_0$ phase to 18 ± 1.1 at the end of the $t_1$ phase, $p < 0.001$, **Figure 1(b)**; aura-related disability: from a mean of 4 points in the $t_0$ phase to a mean of 1 point in the $t_1$ phase, **Figure 1(c)**), and 10 patients (55.5%) reported also a reduction of the intensity of headache (VAS: from 7 ± 1.3 in the $t_0$ phase to 4.2 ± 0.9 at the end of the $t_1$ phase, $p < 0.001$; **Figure 1(d)**). These effects were documented at the end of the first month of Aurastop assumption in 12 patients (66.6%) and was maintained thereafter.

None of the patients reported any adverse events related to treatment.

## 4. Discussion

The results of the present study indicate that all the pre-selected clinical endpoints, including the frequency and the duration of MWA attacks, the rate of aura-related disability, as well as the intensity of pain, improved significantly in most of the patients, and, therefore, highlight the efficacy and the safety profile of the combination of *Tanacetum parthenium*, 5-HTP and magnesium (Aurastop) in high frequency MWA prophylaxis.

These findings lead to speculate that the combination of the 3 molecules might act synergistically on the different pathways involved in migraine pathophysiology, that is neurogenic inflammation, neural transmission, and central sensitization.

These findings are in line with those obtained by Merlo *et al.* [10] in a previous study with a similar design, which suggested a clear efficacy of Aurastop in the treatment of patients with MWA, in terms of reduction of the number of headache days (from 9.1 ± 2.0 before treatment to 3.2 ± 1.8 post treatment), number of attacks per month (from 6.0 ± 1.2 to 2.4 ± 1.1), pain intensity (in a visual analogical scale [VAS]: from 7 ± 1.0 to 3.2 ± 0.7), and number of drug doses for acute treatment (triptans, simple analgesics or in combination) monthly assumed by each patient (from 9.5 ± 1.8 to 2.2 ± 1.1).

Similarly, Zavarise *et al.* [9] recently documented the efficacy of this combination of molecules on the aura phenomena, when assumed soon after the occurrence of the first aura manifestations. Actually, the results demonstrated a reduction of >50% of aura duration (33.6 ± 10.1 minutes vs 9.4 ± 6.2 minutes), of overall disability (5 [4 - 5] vs 1 [1 - 2]), as well as a modification of the clinical features of aura and headache after treatment with Aurastop®. These results are all in agreement with those reported by Dalla Volta *et al.* [12] on behalf of the Italian Society for the Study of Headache (SISC) based on a population of 200 patients who assumed Aurastop at the beginning of the aura phenomena.

## 5. Conclusion

In spite of the obvious methodological limitations of this observational study due to the absence of a placebo group, our findings emphasize the potential effect of Aurastop® on the complex pathophysiological mechanisms of MWA. The combination *Tanacetum parthenium* + 5-HTP + magnesium appears to be a promising alternative therapy for MWA prophylaxis in patients with high frequency of attacks, with an excellent safety profile. Further clinical trials are needed to investigate its potentials in preventing migraine, either alone or in combination with other molecules.

## Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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