An Extract of *Petasites hybridus* is Effective in the Prophylaxis of Migraine

Werner Grossmann, MD, and Hanns Schmidramsl, MD

ABSTRACT

OBJECTIVE: Migraine is still an unsolved problem. This clinical trial investigates the efficacy and tolerance of *Petasites hybridus* in the prophylaxis of migraine. METHODS: A randomized, group-parallel, placebo-controlled, double-blind clinical study was carried out with a special CO_2 extract from the rhizome of *Petasites hybridus*. Following a four-week run-in phase, 60 patients received either the special *Petasites hybridus* extract Petadolex or placebo at a dosage of two capsules (each capsule contains 25 mg) twice daily over 12 weeks. Outcome variables included the frequency, intensity and duration of migraine attacks as well as any accompanying symptoms. RESULTS: The frequency of migraine attacks decreased by a maximum of 60 percent compared to the baseline. This reduction in migraine attacks with Petadolex was significant ($p < 0.05$) compared to placebo. No adverse events were reported. Petasites was exceptionally well tolerated. CONCLUSIONS: The results suggest that migraine patients can benefit from prophylactic treatment with this special extract. The combination of high efficacy and excellent tolerance emphasizes the particular value that *Petasites hybridus* has for the prophylactic treatment of migraine.

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Introduction

The pathophysiology of migraine is still an unsolved problem. In the past, a so-called vascular hypothesis and a neurogenic hypothesis dominated. For Thomas Willis,[1] the basis of migraine was a disturbance of cerebral circulation.[1] Liveing,[2] on the other hand, considered the vascular component to be of secondary importance.[2] He associated this painful phenomenon with an epileptiform activity or "nerve storms." In 1938, Wolff and co-workers formulated the vascular hypothesis by proposing that migraine headache is caused by vasodilatation of the extracranial vessels, whereas neurological symptoms result from intracranial vasoconstriction.[3]

In the last years, new data brought these two hypotheses into discussion, suggesting that migraine headache develops primarily from yet unidentified metabolic or neurophysiological events, closely associated with the distribution of trigeminal nerve fibres innervating meningeal vessels, on the one hand, and leading to an increased activity of the serotonergic raphe nuclei in the brain stem, on the other hand.[4] In a further step, a vasoconstrictive/vasodilatory process does indeed take place, but it remains unclear whether the process takes place at the same time and in the same vessel.[5-7] The increased serotonergic activity and maximal vasodilatation lead

Werner Grossman, MD – Department of Neurology, Municipal Hospital, München-Harlaching. Correspondence address: Städtisches Krankenhaus München-Harlaching, Abteilung Neurologie, Sanatoriumsplatz 2, D-81545 München, Germany.

Hanns Schmidramsl, MD – Krankenhaus für Naturheilwesen, München, Germany.

to a process in which a large number of different substances are involved, e.g. PGE_2, polypeptide neurotransmitters, albumin, as well as endorphin, histamine, substance P, arachidonic acid, extravasation of lymphocytes and so on.[8,9]

Altogether, this results in a sterile neurogenic inflammation – a process that gives us today a much better understanding of different metabolic disturbances. In the case of migraine, neurogenic inflammation stimulates the pain-mediating C fibers, which then project the increased activity back to the trigeminal nerve system. What emerges from this picture is that vasoconstriction and neurogenic inflammation are two main steps in the generation of migraine headache.

Petasites hybridus is a remedy that can be traced back about 900 years, and has been used safely and effectively in modern medicine since the middle of the century. Its pain-relieving effect has been demonstrated in clinical reports of patients receiving the preparation for several weeks.[10-16]

Petadolex is an extract of the rhizome from *Petasites hybridus*, and petasine and isopetasine are the main components.[17] It has been shown that petasine and isopetasine are strong vasodilatory substances, whereby this effect on smooth muscle preparations in vitro is equivalent to papaverine.[18,19] Even more important may be the finding from pharmacological studies that both components exert a highly potent anti-inflammatory effect through inhibition of leukotriene synthesis.[20,21] These clinical and experimental findings served as the pharmacological basis of the present clinical study to confirm the efficacy and tolerability of *Petasites hybridus* in the prophylaxis of migraine with and without aura.

Methods and Patients

The trial was conducted as a randomized, group-parallel, placebo-controlled, double-blind clinical study. It consisted of a four-week run-in phase with no trial medication, followed by a 12-week therapy phase during which either *Petasites hybridus* (Petadolex, Weber & Weber GmbH & Co. KG, Germany) or placebo was administered at a dosage of two capsules twice daily. Each capsule of the trial drug contained 25 mg of a CO_2 extract from the rhizome of *Petasites hybridus*. The extraction method achieves a reduction in the quantity of pyrrolizidine alkaloids to below the detection limit. This meets the requirement of the German Health Authority; i.e., the BfArM (Bundesinstitut für Arzneimittel und Medizinprodukte).[22]

The study was carried out at the Department of Neurology of the Municipal Hospital, Munich-Harlaching. All patients enrolled in the study were outpatients. A minimum of three attacks per month within the last three months prior to the start of the study and a minimum of two attacks in the run-in phase after four weeks without trial medication was necessary for recruitment. The inclusion and exclusion criteria were as defined by the International Headache Society in 1988.[23] Patients were seen at four-week intervals. At each visit, they received for the next four-week period a diary into which they were to record the number, intensity and duration of migraine attacks as well as any accompanying symptoms, such as nausea and vomiting etc. The intensity of migraine headache was assessed using a visual analogue scale from 1–10. Patients were asked at the physician interviews for a global assessment of the frequency and the intensity of migraine attacks during the last four-week interval using a three-point verbal scale (improved – unchanged – worse) and to report any adverse effects during the preceding four-week interval. The patient compliance was checked by counting the remaining capsules. The patients were also asked at the last visit for a global assessment, which was documented by them answering the question "Did you benefit from the treatment?"

The primary efficacy variable was defined as the frequency of migraine attacks per four weeks. Secondary efficacy variables were the number of migraine days, duration and intensity of migraine attacks. Each patient underwent a complete physical and neurological examination, blood pressure measurement and blood analysis (total blood cell count, GOT, GPT, bilirubin) at the beginning and at the end of the study, as well.

Statistical Analysis

The Student's t-test was employed to analyze these efficacy variables; i.e., testing the mean differences of independent random samples between the treatment groups. In addition, the primary efficacy variable "frequency of attacks per month" was evaluated by means of the non-parametric test of Cochran, Mantel and Hänszel.[24] The Chi-square test was employed to analyze the supplementary criteria (e.g. migraine-accompanying symptoms, adverse events and safety laboratory) for significant differences within, as well as between the groups.

Results

A total of 60 patients (28 male, 32 female) were included in the study, with 58 completing it. According to the randomization list, 33 patients (mean age 28.6 ± 9.6 years) were allocated to the drug group and 27 (mean age 29.8 ± 8.5) to the placebo group. Forty-two of the patients had taken acute migraine medication before the study entry, 15 patients had used prophylactic treatments before; however, none had used the Petasites extract before. At baseline, four weeks after study entry, all patients complied with the inclusion and exclusion criteria.

At baseline, the mean number of migraine attacks was 2.9 ± 1.2 for the preceding four weeks in the placebo group and 3.3 ± 1.5 in the drug group. Compared to baseline, the frequency of attacks with the trial drug decreased during the study by a maximum of 60 percent. After four weeks of treatment, Petadolex reduced the frequency of attacks from 3.3 ± 1.5 to 1.8 ± 0.8 attacks per month, after eight weeks to 1.3 ± 0.9, and after 12 weeks to 1.7 ± 0.9, respectively. Following

Figure 1a.

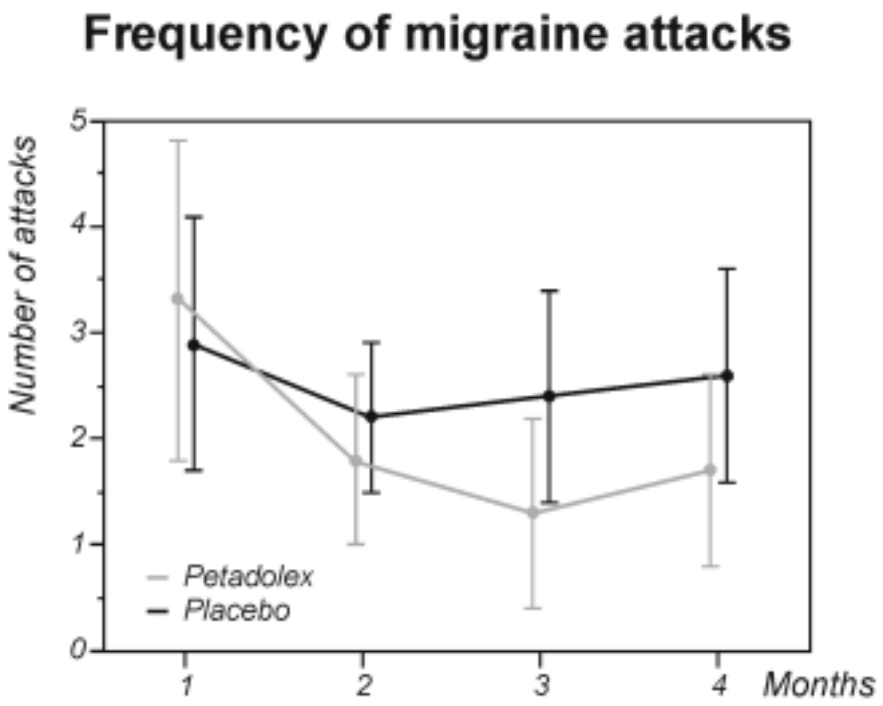
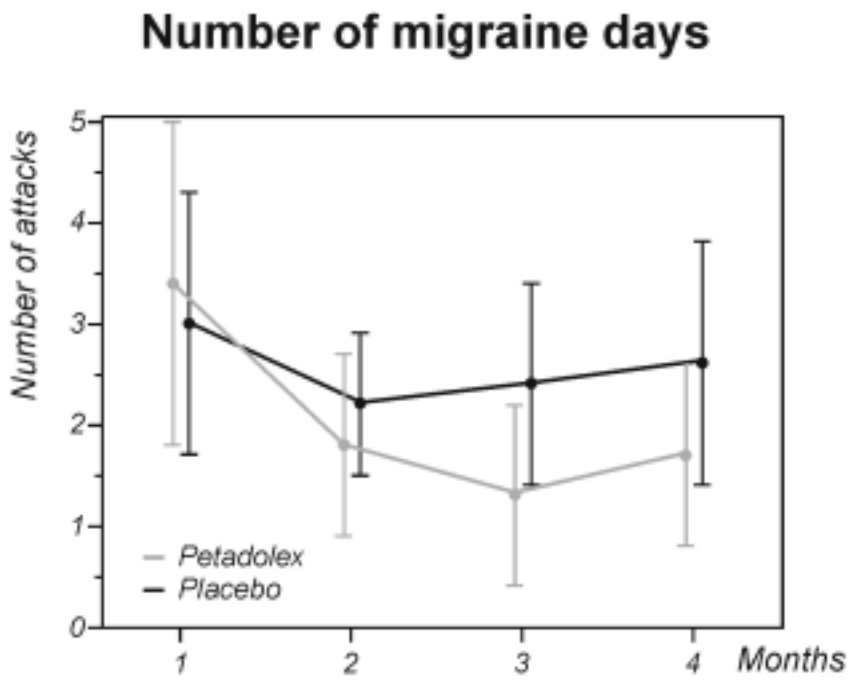


Figure 1b.



placebo, the frequency of attacks decreased from 2.9 ± 1.2 at baseline to 2.2 ± 0.7 after four weeks of treatment, to 2.4 ± 0.8 after eight weeks, and to 2.6 ± 1.1 after 12 weeks, respectively. The reduction in the frequency of migraine attacks with Petadolex was statistically significant ($p < 0.05$) from four-week treatment through to the end of the study when compared to placebo (Figure 1a).

Analogous to the results for frequency of migraine attacks, the number of migraine days per four weeks decreased with Petadolex also significantly compared to placebo over the treatment course (Petasites: from 3.4 ± 1.6 at baseline to 1.7 ± 0.9 days after 12 weeks, placebo: from 3.0 ± 1.3 to 2.6 ± 1.2 days, $p < 0.05$, Figure 1b).

It is noteworthy that five patients on Petadolex reported no attacks during all the following eight weeks of treatment, and three of these patients remained migraine-free up to the end of the study. Four of these patients had a history of five attacks in the run-in observation phase. In contrast, all of the patients on placebo reported at least one attack throughout the treatment phase.

The intensity and duration of migraine headache were also diminished, but these results were statistically significant only at the end of the eighth week after the start of therapy. In the drug group, the mean intensity per month decreased from 4.3 ± 0.9 at baseline to 2.8 ± 1.9 after eight weeks of treatment, and in the placebo group from 4.1 ± 0.8 to 3.8 ± 1.0 ($p < 0.05$). At the end of the treatment phase, pain intensity was up again to 3.2 ± 1.4 in the drug group and to 3.8 ± 1.1 in the placebo group (Figure 2a). The duration of migraine attacks was reduced from 9.6 ± 3.0 at baseline to 56.2 ± 3.4 hours after eight weeks of treatment with Petadolex, and in the placebo group from 9.2 ± 3.9 to 8.2 ± 2.3 hours ($p < 0.05$). The duration of migraine attacks at the end of the treatment phase went up again to 7.2 ± 3.3 in the drug group and to 8.8 ± 2.8 in the placebo group, respectively (Figure 2b). This renewed rise in pain intensity and duration at the end of the third month of treatment with Petasites is noteworthy and at first difficult to interpret.

The mean number of accompanying symptoms was significantly reduced by Petadolex from 18.0 ± 6.6 symptoms at the run-in phase to 9.6 ± 3.1 at the end of the treatment, whereas the finding for the placebo went

Figure 2a.

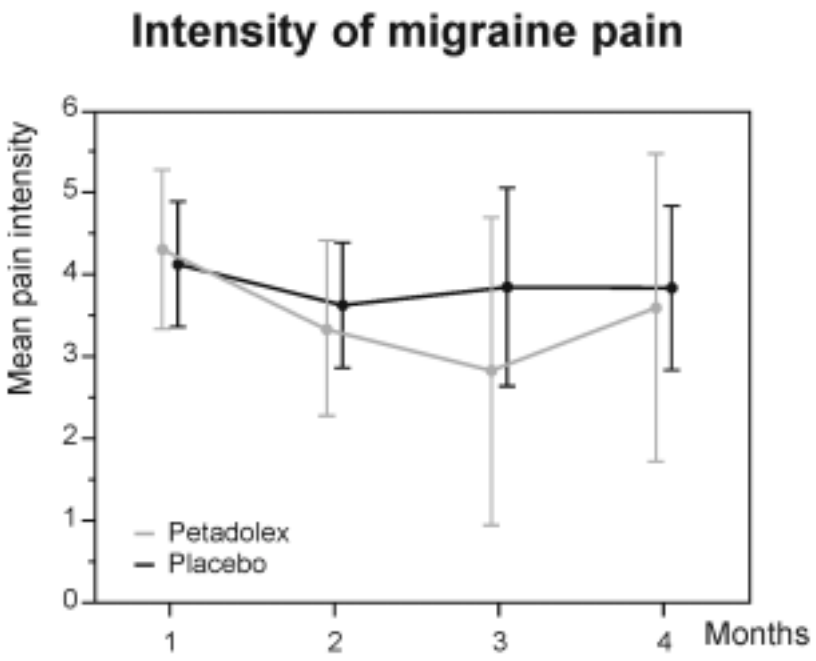
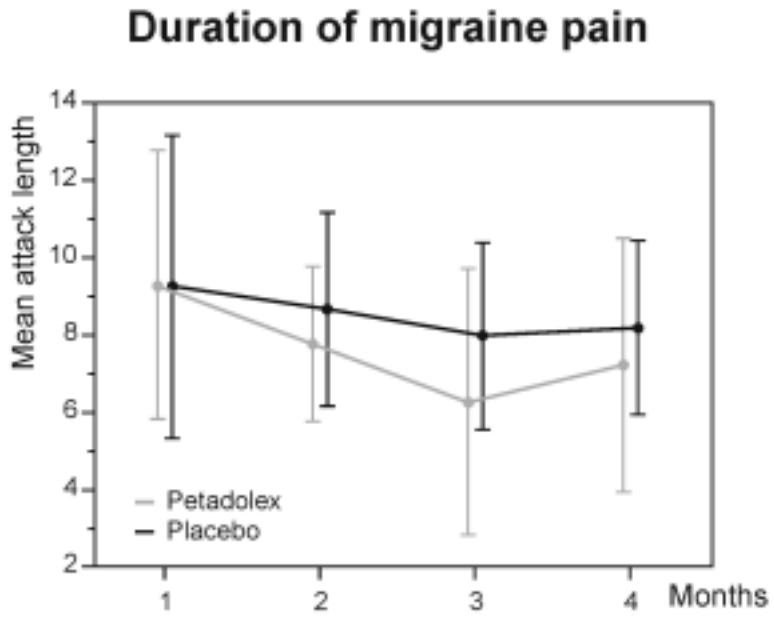


Figure 2b.



Petadolex answered this question with "yes", eight with "no" and in the placebo group, seven patients answered "yes", and 20 "no". The difference was statistically highly significant ($p < 0.005$).

Of the patients who were treated with *Petasites hybridus*, 12 reported that they took fewer analgesics, and 19 patients reported an increased or unchanged use. With placebo, four patients took fewer analgesics and 23 reported taking more or were unchanged. However, only 30 percent of the patients had used analgesics at all for the treatment of acute pain. Therefore, it is not surprising that there was no significant difference between drug and placebo.

It should be emphasized that the Petasites preparation was exceptionally well tolerated. No adverse events were reported in the drug group. Additionally, eight female patients in the drug group reported marked relief of dysmenorrhoic pain. Physical examinations, blood pressure measurements as well as blood analyses of both groups of patients did not show any change over the treatment phase.

Two patients dropped out of the drug group. One stopped taking the medication because of a suspected pregnancy. The other one was not willing to complete the study and gave no reasons for her decision.

Discussion

The results of this study demonstrate that the special extract of *Petasites hybridus* is effective in the prophylactic treatment of migraine. The significant reduction in the frequency of attacks and number of migraine days is comparable to other agents considered effective for migraine prophylaxis, such as b-blockers,[25,26] calcium antagonists, e.g. flunarizine,[27-29] cyclandelate[30] as well as serotonin antagonists, e.g. pizotifen.[31,32]

The special Petasites extract reduced the frequency of attacks by a maximum of 60 percent as compared to baseline. If the subgroup with at least three attacks per month at baseline is analyzed, the reduction is even more pronounced. This result suggests that the special Petasites extract may be more effective in the prophylaxis of migraine in patients with a higher frequency of attacks.

Regarding the intensity and duration of pain, the results obtained from the patients' diaries revealed a statistically significant difference between the drug and placebo only at the end of the second month, but not at the final visit. In contrast, the patients' assessment from the physician interviews showed a significant improvement in the intensity of migraine headache compared to baseline over the whole treatment phase. Moreover, the increase in duration and intensity of the attacks at the end of the treatment period, as recorded in the patients' diaries, is in strong contrast to what is commonly found in clinical practice. The typical observation is namely that migraine patients who accept a prophylactic treatment for months usually experience more frequent and more severe attacks. Patients have been treated in daily clinical practice with 2 x 2 and in some cases also with 3 x 2 capsules per day, and yet absolutely no renewed increase in pain intensity has been reported for a large number of the patients. The effect, as observed in this study, may have been due to the small number of study participants and should be re-evaluated in a more extensive clinical trial. A large US-UK-German multicentre study has therefore been started. On the other hand, these observations are comparable with those reported for flunarizine, which had no influence on the duration and severity of migraine attacks.[28]

The pharmacological mechanism for the therapeutic effect of the special Petasites extract remains to be elucidated. The inhibition of leukotriene synthesis by petasine and isopetasine and the vasodilatory effect may contribute to the efficacy. In any event, this suggested mechanism agrees very well with our present comprehension of migraine pathophysiology.[4]

The study demonstrates a remarkable patient acceptance of this particular herbal drug and a high motivation of the patients to cooperate. With regard to the absence of adverse events, the special Petasites extract is unique compared to all other prophylactic drugs. A 1998 summary of the migraine literature states that "no single prophylactic drug is superior when potential side-effects are also considered."[33] Serious side-effects have been reported for β-blockers – the drugs of first choice for migraine prophylaxis – in over 30 percent of patients,[34,35] and these side-effects include orthostatic hypotension, fatigue, depression, impaired memory, sleep disorders, gastrointestinal complaints, impotence, etc.[36] Migraine patients may therefore benefit from prophylactic treatment with the Petasites preparation studied here. A further advantage is that this preparation may be used safely in combination with other therapies for acute and prophylactic treatment of migraine.

Conclusions

These results of the efficacy of *Petasites hybridus* suggest that migraine patients can benefit from prophylactic treatment with this phytodrug. The combination of high efficacy and excellent tolerability emphasizes the particular value that *Petasites hybridus* has for the prophylactic treatment of migraine.

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