Migraine Prevention in Children and Adolescents: Results of an Open Study With a Special Butterbur Root Extract

Raymund Pothmann, MD; Ulrich Danesch, PhD

Objective.—To explore the role of a special butterbur root extract for migraine prevention in children and adolescents with severe migraines.

Background.—Two randomized and placebo-controlled trials with a total of 289 migraine patients have demonstrated the efficacy and safety of a special butterbur root extract in the reduction of migraine attacks in adults. We studied whether butterbur had the potential as an efficient and well-tolerated migraine preventive in children and adolescents.

Design/Methods.—108 children and adolescents between the ages of 6 and 17 were included in a multicenter prospective open-label study. Participants suffered from migraines diagnosed according to IHS classifications for at least 1 year. Patients were treated with 50 to 150 mg of the butterbur root extract depending on age for a period of 4 months. Treatment progression was recorded in migraine journals especially designed for children and adolescents.

Results.—77% of all patients reported a reduction in the frequency of migraine attacks of at least 50%. Attack frequency was reduced by 63%. 91% of patients felt substantially or at least slightly improved after 4 months of treatment. About 90% of each, doctors and patients, reported well-being or even improved well-being. Undesired effects (7.4%) included mostly eructation. No serious adverse events occurred and no adverse event caused a premature termination.

Conclusions.—The results and low rate of adverse events in this open prospective migraine prevention study in children and adolescents are similar to the results of two multicenter placebo-controlled butterbur studies in adults. Butterbur root extract shows a potential as an effective and well-tolerated migraine prophylaxis also for children and teenagers.

Key words: butterbur, migraine, prevention, children, adolescents

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Migraines are a common problem in children of all ages. Symptoms can vary dramatically in terms of character and severity, from brief self-limited headaches to prolonged events with complex neurologic and systemic symptoms. It is estimated that migraine occurs in about 3% to 7% of all children.[1] Recurrent headaches can be a significant source of stress for patient and parents, and disruptive regarding school obligations. Treatment of migraine in children consists primarily of avoidance of triggers, rest, and simple analgesics. Only ibuprofen and nasal sumatriptan have been well documented in clinical trials as an efficient acute medication for children.[2,3] Prophylactic treatment of migraine is recommended, when more than three attacks per month occur which do not respond well to abortive therapy and/or side effects of abortive therapy are intolerable, when attacks last longer than 48 hours, and when patients experience attacks to be intolerable.[4] Unlike the situation with adult migraine however, only a very few controlled trials have investigated the prophylactic treatment of migraine in children. Only

From the Klinikum Heidberg, Zentrum für Kinderschmerztherapie, Hamburg, Germany (Dr. Pothmann); and Weber & Weber GmbH & Co, KG, Research & Development, Herrsching, Germany (Dr. Danesch).

Address all correspondence to Dr. Raymund Pothmann, MD, Klinikum Heidberg, Zentrum für Kinderschmerztherapie, Tangstedter Landstrasse 400, 22417 Hamburg, Germany.

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flunarizine has been shown to be effective in more than one double-blind, placebo-controlled trial.[5,6] Some evidence also exists for propranolol and pizotifen; however, the results from different trials are contradictory.[7-11] For all other drugs studied in migraine prophylaxis, the results remain vague or suggest inefficacy.[1,12] Since most drugs seem to be ineffective in children, an effective and tolerable prophylaxis is of great importance for this group of patients.

Butterbur or *Petasites hybridus* is a native European plant that flourishes along the banks of streams and in other moist areas. Butterbur has a long list of traditional use dating back to ancient times. The medicinal properties of the plant were rediscovered since the middle of last century. Its spasmolytic and analgesic effects are used in conditions like migraine, asthma, urinary tract spasms, and back pain, and are thought to be mainly attributed to a group of sesquiterpenes, mainly the petasins.[13-18] Therapeutically, Petadolex® is primarily used for migraine prevention. Two randomized, placebo-controlled migraine prevention trials with a total of 289 patients demonstrated the safety and efficacy of the butterbur root extract in adults.[19,20] Those results prompted us to explore a possible role for butterbur in the prevention of migraine in children also. Since approval of placebo-controlled trials in children is very hard to obtain by an ethical review board in Germany, an open study was performed.

PATIENTS AND METHODS

Between April 1998 and July 2002, a total of 112 patients entered the open-label prospective trial in five pediatric clinics and 13 practices. Four patients did not meet inclusion criteria and were excluded from analysis. The intention to treat study population consisted of 29 children between the ages of 6 and 9 years and 79 adolescents between the ages of 10 and 17 years. Migraine with or without aura was diagnosed according to International Headache Society (IHS) criteria.[4] Only patients with migraine for at least 1 year and a minimum of three migraine attacks per month in the 3 months preceding the trial and/or significant severity and duration (at least 0.5 to 1 day) of attacks were included into the trial. Exclusion criteria were use of prophylactic migraine medication within three months prior to study baseline, a history of effective treatment with the special butterbur root extract Petadolex® and serious concomitant illness which may confound assessments.

Prior to the start of the trial, notification was made to the German regulatory authorities (BfArM) and to the German National Association of Statutory Health Insurance Physicians (Kassenärztliche Bundesvereinigung). Informed consent or IRB approval for the open trial is not required by German Drug Law because patients were treated with an approved drug in an approved indication as part of a regular or routine therapeutic treatment. Trial procedures complied with requirements of the current European Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) where applicable

Children and adolescents were treated for 4 months with 25 mg capsules of the special butterbur root extract Petadolex® (manufactured by Weber & Weber GmbH & Co, KG, Germany). Capsules contain a extract of the rhizome of *Petasites hybridus* with supercritical CO_2 as solvent (drug:extract ratio, 28:44). The extract contains a minimum of 15% petasins. Pyrrolizidine alkaloids are removed by the extraction method according to the German pharmacovigilance requirements. The finished product (soft gelatine capsule) has been available in Germany since 1972 as a pharmacy medicine under the regulations of respective national drug laws. In the United States, Petadolex® has been available since 1997 as an herbal supplement. Capsules were taken twice daily, in the morning and in the evening, with meals. Dosing was at the discretion of the investigator, the following dosing recommendations were made: months 1–2: 2 × 1 capsule (6–9 years of age) or 2 × 2 capsules (10–17 years of age) daily. Months 3–4: responders continued with the previous dosing, nonresponders increased the dose to 3 × 1 capsule (6–9 years of age) and 3 × 2 capsules (10–17 years of age). Intake of the extract had to be documented daily in the diary. Visits took place 2 and 4 month after the start of the trial, respectively. The following variables were documented either by the patient in the diary or by the physician in the case record form (CRF): number, duration, and severity (10-point visual scale) of migraine attacks, rating of severity of associated symptoms, rating of physical impairment (4-point verbal scale) and general impairment (10-point

Table 1.—Descriptive Statistics of Baseline Demographic and Anamnestic Variables

		Patients 6–9 Years (n = 29)			Patients 10–17 Years (n = 79)			Total (n = 108)
Age (years)		8.0 ± 0.9	(6 8 9)	29	12.3 ± 1.9	(10 12 17)	79	11.8 ± 2.6
Sex	male	16 (55.2%)			43 (54.4%)			59 (54.6%)
	female	11 (37.9%)			36 (45.6%)			47 (43.5%)
	n.a.	2 (6.9%)			–	–		2 (1.9%)
Height (cm)		134.3 ± 9.2	(105 135 150)	29	155.8 ± 13.6	(120 156 186)	76	149.9 ± 15.8
Weight (kg)		32.0 ± 7.7	(20 30 53)	28	47.0 ± 15.1	(26 44 100)	77	43.0 ± 15.0
Migraine with aura		4 (13.8%)			16 (20.3%)			20 (18.5%)
Migraine without aura		22 (75.9%)			61 (77.2%)			83 (76.9%)
Both types		1 (3.4%)			1 (1.3%)			2 (1.9%)
Diagnosis not available		2 (6.9%)			1 (1.3%)			3 (2.8%)
Duration of migraine prior to study (months)		25.9 ± 14.4	(12 24 72)	28	37.9 ± 20.6	(12 36 108)	78	34.8 ± 19.9
Migraine attacks during last 3 months (n)		9.4 ± 8.5	(2 9 48)	29	9.7 ± 10.0	(1 8 72)	78	9.6 ± 9.6
Duration of latest migraine attack (h)		9.6 ± 12.2	(1.5 6 48)	26	10.2 ± 10.8	(0.5 6 60)	76	10.0 ± 11.1
Concomitant	no	23 (79.3%)			66 (83.5%)			89 (82.4%)
illnesses	yes	6 (20.7%)			13 (16.5%)			19 (17.6%)
Migraine drug	no	14 (48.3%)			30 (38.0%)			44 (40.7%)
therapy	yes	15 (51.7%)			49 (62.0%)			64 (59.3%)
Other migraine	no	28 (96.6%)			68 (86.1%)			96 (88.9%)
treatments	yes	1 (3.4%)			11 (13.9%)			12 (11.1%)
Migraine	no	29 (100%)			73 (92.4%)			102 (94.4%)
prophylaxis	yes	0 (0%)			6 (7.6%)			6 (5.6%)

Values followed by brackets are means ± SD, with minimum, median, and maximum in brackets, and valid cases after the brackets. All values are rounded. n.a. = not available.

visual scale) by the patient, global evaluation of efficacy as well as global evaluation of safety by both the physician (clinical global impression scale), and patient (6-point verbal scale), concomitant medication. Investigators were instructed to actively ask for adverse drug reactions at each visit. All adverse drug reactions were recorded in a separate standard form, which was part of each patient's CRF. The diaries were especially designed for children. In accordance with IHS guidelines for clinical migraine studies, frequency and duration (latest attack documented in diary) as well as therapy responders were chosen as primary variables to assess the effectiveness of prophylactic medication with the butterbur extract. Statistical analysis was by descriptive means, depending on the type of variable (binomial, discrete, continuous), means, standard deviations, minima, maxima, medians, and other measures of distribution were calculated.

RESULTS

Demographic baseline data, medical history of migraine, concomitant illnesses, and previous migraine treatments of the study population are listed in Table 1. Of 112 patients who entered the open-label prospective trial four patients were excluded from analysis because they did not meet inclusion criteria (no migraine, migraine for only 8 months, diabetes mellitus, prior successful treatment with butterbur). Analysis of primary efficacy variables is listed in Table 2. The number of monthly migraine attacks was substantially reduced after 4 months of treatment with the butterbur extract in relation to prestudy baseline and comparable in both age groups. Starting with mean baselines of 9.4 and 9.7 attacks during the last 3 months prior to study entry, children 6–9 years and those 10–17 years experienced only means of 4.0 and 5.8 attacks during 4 months of therapy, respectively. The attack reduction in the total sample population was 63.2%.

Table 2.—Descriptive Analysis of Primary Efficacy Variables (Attack Frequency, Therapy Responders, Attack Duration) After 4 Months of Treatment in Relation to Baseline

	Patients 6–9 Years (n = 29)			Patients 10–17 Years (n = 79)			Total
Attack frequency (n)	4.0 ± 3.9	(1 2 15)	21	5.8 ± 16.2	(0 2 124)	59	5.3 ± 14.0
Relative reduction of attack frequency (%)	−67.0 ± 28.3	(37 78 92)	21	−61.9 ± 53.3	(187 80 100)	58	−63.2 ± 47.7
Responder	18 (85.7%)			43 (74.1%)			61 (77.2%)
Nonresponder	3 (14.3%)			15 (25.9%)			18 (22.8%)
Duration of migraine attacks (h)	7.3 ± 9.8	(1.0 3.7 35.0)	16	6.4 ± 6.2	(1.0 5.0 35.0)	37	6.5 ± 7.3
Shortened attack	10 (66.7%)			22 (61.1%)			32 (62.7%)
Unchanged attack	1 (6.7%)			5 (13.9%)			6 (11.8%)
Prolonged attack	4 (26.7%)			9 (25.0%)			13 (25.5%)

Values followed by brackets are means ± SD, with minimum, median, and maximum in brackets, and valid cases after the brackets.

In accordance with IHS guidelines for clinical trials, response as a measure of clinical relevance was defined as a reduction of at least 50% in monthly migraine attack frequency. About 85.7% (18 out of 21) of the younger and 74.1% (43 out of 58) of the older patients were responders. There were 77.2% responders in the total sample population (Table 2).

Prophylactic treatment with the butterbur extract also reduced the duration of migraine attacks from about 10 hours on average before the study to about 7 hours under treatment. Comparing intraindividually the duration of the last attack before study entry with that of the last attack during the study, 66.7% (10 out of 15) of the children and 61.1% (22 out of 36) of the adolescents benefited from treatment in terms of reduced duration. However, also approximately 25% of patients experienced a prolonged attack under treatment (Table 2).

Patients or parents rated overall efficacy in terms of migraine status at the end of the trial by a 6-point verbal scale. They were asked for the current status of migraine in comparison to the prestudy situation, thereby allowing also for ratings of worsening. About 81.6% (71 out of 87) of all patients reported substantial improvement of their migraine compared to the situation prior to the study. None of the patients reported worsening of migraine and one patient each per age-group reported premature termination of treatment due to lack of efficacy (Figure 1). Efficacy ratings by the investigators using a modified efficacy/tolerability CGI-Index confirmed the patients' evaluation (data not shown).

For an evaluation of tolerability patients were asked about their well-being (6-point verbal scale). About 91.8% (78 out of 85) of all patients felt well or even better than before the study. Only one patient each in both age groups felt substantially impaired by the treatment. One patient was erroneously recorded as "premature termination" although termination was not due to lack of tolerability according to evaluation of the complete case records (Figure 2). The investigators evaluated tolerability (modified efficacy/tolerability CGI-Index) in 98.2% of the patients as excellent (data not shown).

Safety and tolerability of treatments were also assessed by recording of adverse events. A total of eight adverse events were reported in eight patients (7.4% of the total sample), four concerned mild eructation—a well-known side effect of the butterbur extract. Other adverse events were of mild or moderate intensity. The investigator rated three of four cases of mild eructation, one case of moderate nausea and one case of moderate abdominal pain to be "probable" related to Petadolex® intake (Table 3). None of these adverse events lead to withdrawal from the study. No serious adverse events or deaths were reported.

COMMENTS

The authors are aware that the uncontrolled open-label design of this study does not allow to draw

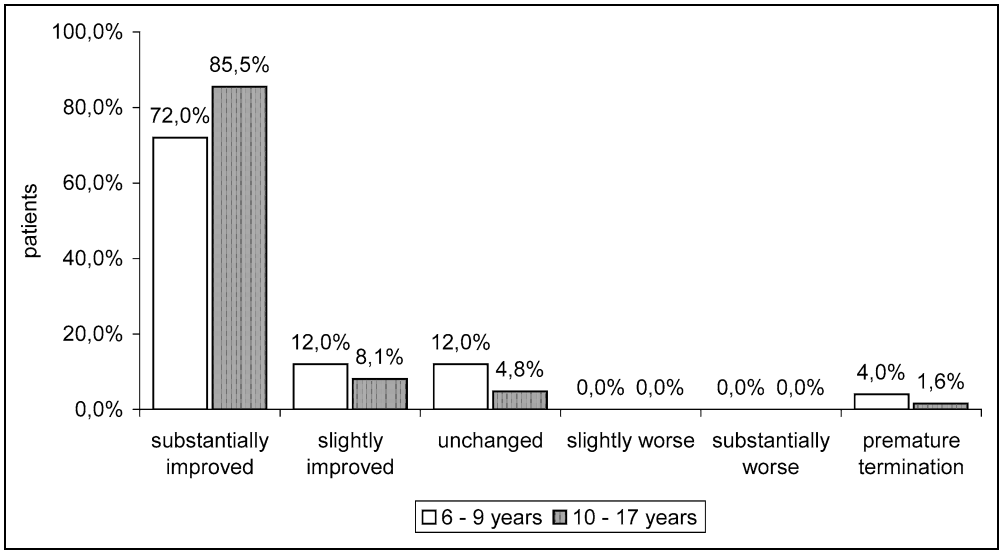

Fig 1.—Global judgment of efficacy of prophylactic butterbur treatment by patients: current status of migraine in comparison to the prestudy situation.

definite conclusions regarding efficacy and tolerability of treatment by itself. However, two recent placebo-controlled, randomized, and double-blind trials[19,20] with the same butterbur extract have shown similar results regarding efficacy variables and tolerability in adults.

The number of migraine attacks of children and adolescents suffering from severe migraine were substantially reduced under the butterbur root extract in both age groups. Improvement was even more pronounced looking at medians (baseline: 9 and 8; end of study: 2 and 2) rather than means (baseline: 9.4 and 9.7; end of study: 4.0 and 5.8) of attack frequencies. This indicates a skewed distribution caused by single outliers like one patient who allegedly suffered from 124 attacks under treatment. It is noteworthy that 12 out of 59 of the adolescents were even free from any attacks under treatment and more than half of the patients in both age groups suffered from only a maximum of two attacks during 4 months of treatment. A pre and post comparisons was not possible for severity of migraine attacks since anamnestic data were not

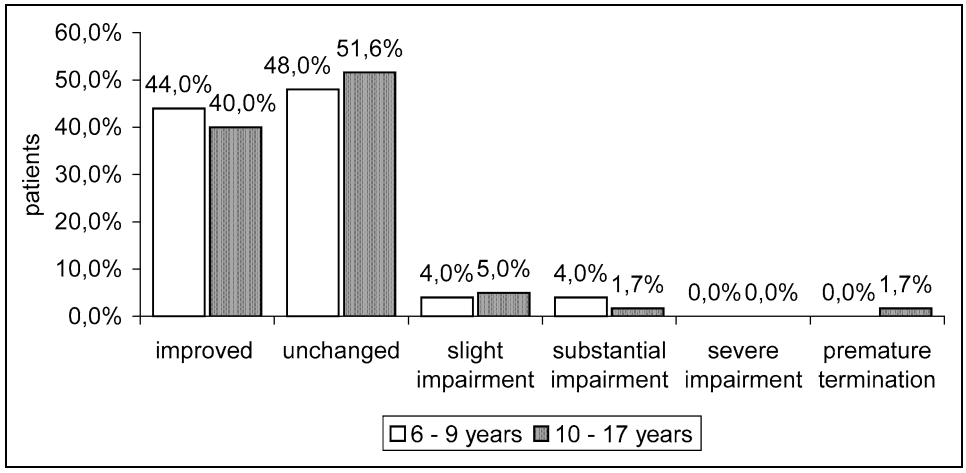

Fig 2.—Global judgment of tolerability of prophylactic butterbur treatment by patients: current status of well-being in comparison to the prestudy situation.

Table 3.—Adverse Events and Causality

Adverse Event	Causal Relation With Butterbur
Nose bleeding	No
Influenza infection	No
Mild eructation (4 cases)	3x probable, 1x uncertain
Nausea	Probable
Abdominal pain	Probable

available. However, 67% of the children and 49% of the adolescents reported in the diaries that they felt that attack severity had been reduced by the butterbur treatment. We also looked at the number of patients who experienced at least a 50% reduction in monthly migraine attacks as an additional efficacy measure. Both age groups revealed a significant response to the prophylactic treatment.

The majority of drugs used for adult migraine prevention has mostly been ineffective or had mixed results in children.[1] Most of the trials have been done with flunarizine. Flunarizine is the only migraine prophylactic that has been shown to be effective in more than one randomized trail.[5,6] In addition, efficacy of flunarizine has also been reported in few small open trials.[21,22] In these open-label trials with 13 children each, flunarizine was reported to be effective in 54% and approximately 80% of the children, respectively. The butterbur trial was done with a much higher patient number (n = 108) allowing for additional power. The responder rate (74% and 86% depending on age) was also higher, at least compared to one of the two flunarizine trials. Based on that open-trial comparison, butterbur seems to be equal or even superior to flunarizine. In general, open trials for migraine prevention in children are very rare and suffer from a low number of treated patients, results are hard to generalize. In one larger open trial with pizotifen in 187 children (mean age 8.5 years), a 70% responder rate was found.[23] However, results with pizotifen in randomized trials were contradictory.[24,25]

In two randomized placebo-controlled trials in adults the butterbur extract was associated with a statistically significant improvement over placebo in mean monthly attack count, and in the number of patients showing a 50% or greater improvement in attacks in adults.[19,20] Though cross-study comparisons may not be valid, this level of treatment effect in adult patients is broadly comparable to results obtained with prescription preventive medications.[26-29] For example, after 4 months of treatment in adults the reduction in migraine frequency for the butterbur extract 75 mg b.i.d. was 51% compared to 32% for placebo, the responder rate was 68% for butterbur and 49% for placebo.[20] In the present open trial in children and adolescents, reduction in frequency (61.9% to 67%) as well as responder rates (74.1% to 85.7%) were higher than in adults and also higher compared to a randomized trial with flunarizine in children (66%).[6] It is known that open trials tend to give better results than randomized placebo-controlled trials. The fact that the efficacy variables are higher in the open trial and not lower supports the notion that butterbur might be effective in children.

Global ratings by the investigator and patients confirm the efficacy results. The subjective impression of patients as recorded in the headache diary was that reduction of frequency of migraine attacks had been more significant than reduction of duration and severity. This observation is in agreement with data from the randomized and placebo-controlled clinical trial with the butterbur extract.

Few secondary criteria like rating of severity of associated symptoms, rating of physical and general impairment as well as concomitant medication that were to be recorded in the diary by the children could not be analyzed. Entries were only sporadic and mostly missing. However, loss of these additional and minor rating criteria does not have an impact on the outcome of the trial because global evaluation of efficacy and tolerability, which were recorded in the CRF were completely available for analysis.

The mechanisms of action of the butterbur extract in migraine are not known. In vitro studies report that the butterbur extract has anti-inflammatory properties including antileukotriene activity.[18,30-32] Leukotrienes and other inflammatory mediators have been implicated in the inflammatory cascade associated with migraine.[33,34] Another possible site of action involves an effect on calcium channels as demonstrated in vascular smooth muscle and trachea.[35,36]

The butterbur extract was very well tolerated. Four out of the eight adverse events reported in this trial were eructations. Mild eructation is the only significant and well-known side effect of the special butterbur extract. All other adverse events were of mild nature and did not lead to premature termination.

In conclusion, the data reported here confirm the excellent tolerability profile of prophylactic treatment with the butterbur extract which is known from clinical studies and drug-monitoring trials in adults, even in children from 6 years of age at doses from 50 to 150 mg daily. Although the design of this study alone is not sufficient to draw any definite conclusions regarding efficacy of treatment, the sum of available and randomized trial data show a potential of butterbur extract as an effective alternative to established drugs for prophylactic migraine treatment in children and adolescents. The results also suggest that a placebo-controlled trial should be done in children and adolescents to further document efficacy.

Warning: the special butterbur root extract used in this trial (Petadolex®) was purified to remove all pyrrolizidine alkaloids according to the German pharmacovigilance requirements. The use of unpurified extracts contaminated by pyrrolizidine alkaloids that are present in the plant might cause liver damage or liver cancer.

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