

Long-term Efficacy and Safety of Piracetam in the Treatment of Progressive Myoclonus Epilepsy

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Background: Piracetam has been proven to be effective and well tolerated in the treatment of myoclonus in short-term studies.

Objective: To assess its long-term clinical efficacy, 11 patients with disabling myoclonus due to progressive myoclonus epilepsy were treated with piracetam in an open-label study.

Methods: Neurologic outcome (at the 1st, 6th, 12th, and 18th month of treatment) was assessed by an adjusted sum score of the following 3 indices: motor impairment, functional disability, and global assessment of disability due to myoclonus. Severity of other neurologic symptoms (seizure frequency and severity, dysarthria, and gait ataxia) also was assessed. Treatment with piracetam was initiated at a dose of 3.2 g/d that was gradually increased until stable benefit was noted (maximal dose

in the trial was 20 g/d). Concomitant antiepileptic drugs were maintained at their previous dose.

Results: Statistically significant improvement in the total rating score was observed after introduction of piracetam at the 1st, 6th, and 12th month of treatment. Severity of other neurologic symptom scores did not improve significantly. Two patients reported drowsiness during the first 2 weeks of treatment.

Conclusions: Piracetam given as add-on therapy seems to be an effective, sustained, and well-tolerated treatment of myoclonus. In patients with progressive myoclonus epilepsy, the efficacy of the drug increased during the first 12 months of treatment and then stabilized.

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MYOCLONUS consists of sudden, irregular muscle jerks unassociated with loss of consciousness.¹ Progressive myoclonus epilepsy (PME) represents an uncommon epilepsy syndrome caused by a large number of rare specific genetic disorders. In its fully developed form, the syndrome consists of myoclonic jerks, tonic-clonic seizures, mental retardation, and ataxia.² Myoclonic jerks are often difficult to control in these conditions and usually are an important cause of disability in activities of daily living.

Piracetam (2-oxo-1-pyrrolidine-acetamide) a nootropic drug with broad indications and few transient adverse effects has been shown to be an effective antimyoclonic agent with a dose-related effect. Since the first report by Terwinghe et al³ in 1978 in a patient with action myoclonus due to Lance-Adams syndrome, several short-term studies have suggested that piracetam may have a beneficial effect in the treatment of cortical myoclonus regard-

less of the underlying cause.⁴⁻¹¹ We performed a long-term, open-label study of 11 patients who had intractable myoclonus to evaluate the efficacy and the safety of piracetam treatment over an 18-month period.

RESULTS

The total daily maintenance dose of piracetam, given in 2 or 3 doses, ranged from 9.6 to 20 g/d (mean \pm SD, 13.5 \pm 7.2 g/d). Mean \pm SD duration of treatment was 24.1 \pm 3.7 months (range, 18-26 months). All patients completed the follow-up at 18 months. Piracetam was given as an add-on therapy to the following previous drug regimens: valproate sodium, 3 patients; valproate and clonazepam, 5 patients; gabapentin and lamotrigine, 1 patient; valproate, clonazepam, phenobarbital and lamotrigine, 1 patient; and valproate and ethosuximide, 1 patient. Median and range of scores of motor impairment, functional disability, severity of other neurologic symptoms, global assessment of the

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PATIENTS AND METHODS

Eleven patients (8 males and 3 females; age range, 17-36 years; mean \pm SD age, 24.5 ± 5.8 years) who had severe chronic disabling action and spontaneous myoclonus were treated with piracetam added to their previous drug regimen between November 1994 and November 1998. Before the introduction of piracetam treatment control of myoclonus was poor, despite the use of other antimyoclonic agents. Exclusion criteria included pregnancy, breastfeeding, and severe renal impairment.

Myoclonus was secondary to Unverricht-Lundborg disease in 2 patients, Lafora disease in 3 patients, mitochondrial encephalomyopathy with ragged red fibers in 3 patients, and sialidosis type I in 1 patient. In 2 patients with typical clinical features of PME, a specific diagnosis could not be reached despite extensive investigation. Mean \pm SD age at onset was 10.7 ± 6.4 years (age range, 2-26 years), duration of disease ranged between 4 and 22 years (mean \pm SD duration, 13 ± 8 years). All patients had action and spontaneous myoclonus; stimulus sensitivity was noted in 3. Generalized tonic-clonic seizures were present in 8 and absent in 3. Two patients with Lafora disease also had focal occipital seizures. Electroencephalograms were obtained for all patients; somatosensory evoked potentials were obtained in 5 patients and jerk locked back averaging of electroencephalographic activity preceding jerks in 4 patients.

All patients underwent high-resolution brain magnetic resonance imaging using a 1.5-T scanner. Magnetic resonance spectroscopy was performed in 5 patients and

fluorodeoxyglucose F 18–positron emission tomography in 1 patient. Diagnosis was confirmed by genetic analysis or biopsy in patients having Lafora disease, Unverricht-Lundborg disease, and mitochondrial encephalomyopathy with ragged red fibers. Grossly elevated urinary sialoliposaccharide levels and the characteristic cherry-red spot in the fundus supported the diagnosis of sialidosis type I. Patients were assigned to 1 of 3 stages according to the duration of disease, level of disability, and clinical and electrophysiological features: early, intermediate, and late.¹²⁻¹⁴ By dividing the baseline motor impairment due to myoclonus by the duration of the disease in years, a quotient was calculated to reflect the rate of progression. Myoclonus was the primary cause of disability in activities of daily living leading to complete dependence requiring constant assistance for 9 patients and slight assistance for 2 patients who needed some help. Clinical features and findings are summarized in **Table 1**.

Piracetam was obtained in 800-mg capsules, given in increasing dosage, starting with 3.2 g/d divided in 3 doses, then increased by 2.4 g/d every 4 days up to a maximum dose of 20 g/d or until a stable therapeutic effect was evident. The dosage of other antimyoclonic or antiepileptic drugs remained constant.

CLINICAL EVALUATION

All patients were periodically examined by at least one of us before and during treatment over an 18-month period. The presence, frequency, severity, and degree of disability due to myoclonus was evaluated by clinical interviews, neurologic examination, and analysis of videotape recordings

intensity of myoclonus, and adjusted sum score during the 4 follow-up periods are summarized in **Table 3**. The Friedman statistical test showed a significant effect of piracetam treatment on the overall functions in the adjusted sum score and the motor impairment index ($P < .01$). Significant improvement was noted in the resting myoclonus frequency scale ($P < .001$), action myoclonus frequency scale ($P < .003$), action myoclonus severity scale ($P < .001$), and global impression of intensity of myoclonus scale ($P < .001$).

Functional disability score improved from the baseline, but this was not statistically significant ($P < .06$). Among associated neurologic symptoms no statistically significant difference was noticed between baseline and the treatment period ($P < .09$). In 2 patients marked reduction of seizure frequency was observed; but when assessing the effect of piracetam treatment on seizure frequency and severity, no statistical significance was found in the group between the baseline and the treatment period ($P < .36$). With regard to differences encountered between baseline and each follow-up period, Wilcoxon 2-sample rank sum test showed significant improvement ($P < .01$) between baseline and the 1st, 6th, and 12th months of treatment in the following scores: adjusted sum score, motor impairment index, resting myoclonus frequency scale, action myoclonus frequency scale, action myoclonus severity scale, and global impression of intensity of myoclonus (Table 3). The following scales showed a borderline significant difference between the

baseline and the 18th month of therapy with piracetam: adjusted sum score ($P < .04$), motor impairment index ($P < .05$), resting myoclonus frequency scale ($P < .07$), action myoclonus frequency scale ($P < .04$), and action myoclonus severity scale ($P < .07$). The median percentage improvement for each period [(baseline score – treatment score)/baseline score], ranged from 22.3% to 80.6% for the individual test score.

The median improvement of the adjusted sum score improved by a median of 16.6% (range, 1.2%-22.3%) at the first month of treatment, 21.7% (range, 13%-24.1%) at the sixth month, 37.6% (range, 14%-58.3%) at the 12th month, and at 31.3% (range, 13.4%-46.3%) at the 18th month.

Both median improvements and statistical significance of the adjusted sum score showed a trend toward a decrement of the efficacy of piracetam treatment in controlling myoclonus after the 12th month. No significant correlation was found between the degree of improvement or the motor impairment index and the duration of disease or the rate of progression of the disease. The impression of the effect of piracetam on myoclonus assessed by the parents and physicians in the 11 patients, comparing the period before and after treatment, indicated a marked reduction in 3, moderate reduction in 5, and mild reduction in 4. Among those patients with mild reduction, there were 2 patients with advanced Lafora disease and almost continuous myoclonic jerks.

obtained before and during treatment. Clinical benefit was assessed using a modification of the rating scales described by Truong and Fahn¹⁵ for motor impairment, functional disability, severity of other symptoms, global impression of intensity of myoclonus by the investigator, the parents, or the care giver, and global impression of efficacy of treatment by the investigator and the patient. Measurements of these indices were performed on enrollment in the study and after 1, 6, 12, and 18 months of treatment.

Myoclonus was clinically scored in 8 regions of the body (eyes, face, neck, trunk, and all 4 limbs) for frequency (resting and action myoclonus) and severity (action myoclonus). Functional disability in activities of daily living was evaluated in 7 domains: eating (ability to use a fork and knife), swallowing, dressing, speech, hygiene, balance, and presence of falling. Each function was rated on a scale of 0 (worse) to 4 (best). In previous studies^{5,6} "walking" was included in the functional disability score. Since in patients with PME walking may be disturbed by either ataxia or action myoclonus, we evaluated balance (ataxia) and falling (myoclonus) separately to achieve a more sensitive result. Both scores were rated according to severity and interference in activities of daily living on a scale of 0 (worse) to 4 (best). The global impression of intensity of myoclonus achieved from the parents and the physician was rated as follows: 0, none; 1, mild; 2, moderate; 3, marked (causing interference and distress); and 4, severe (causing great distress in activities of daily living). Since most patients had additional neurologic dysfunction, the following accompanying neurologic symptoms were also evaluated: seizure frequency and

severity,¹⁶ dysarthria, and gait ataxia. Seizure frequency was scored as follows: 0, no seizures; 1, less than 1 seizure yearly; 2, at least 1 seizure yearly; 3, at least 1 seizure monthly; 4, at least 1 seizure weekly; 5, at least 1, but less than 10 seizures daily; and 6, more than 10 seizures daily. Seizure severity was defined according to different features: falls, loss of consciousness, and duration of postictal effect in a score of 0 to 4. Dysarthria and ataxic gait were scored as 0, none; 1, slight; 2, mild; 3, moderate; and 4, severe anarthria or imbalance.

The global clinical impression of the efficacy of piracetam treatment was deduced from parents and physician observers: marked control of myoclonus, 75% to 100%; moderate, 50% to 74%; slight, 25% to 49%; no reduction, 0% to 24%; and worsening, 0% worse than the baseline value.⁷

Detailed scores of myoclonus and associated symptoms are listed in **Table 2**. We did not assess stimulus sensitivity and handwriting scores.

STATISTICAL METHODS

The Friedman test was performed to assess statistical differences between the baseline and the treatment followed by Wilcoxon 2-sample rank sum test to evaluate the differences between the baseline and each follow-up period. For the Wilcoxon 2-sample rank sum test (since we are comparing baseline against other time measurements), α was corrected for multiple comparisons and statistical significance was set at $P < .01$. SysStat version 7.01 software (SPSS Science, Chicago, Ill) was used for the analysis.

Piracetam was well tolerated. Two patients reported drowsiness and dizziness during the first 2 weeks of treatment. There was no positive relationship between the dosage and the occurrence of adverse effects. No patient reported diarrhea, a common adverse effect of piracetam when given at a high dosage.

COMMENT

This study demonstrates that piracetam is effective and well tolerated for symptomatic treatment of myoclonus. Significant and clinically relevant improvement was found in the mean sum score of myoclonus rating scales, and particularly in motor impairment and global assessment of intensity of myoclonus subscores. Since in some individuals only low doses were used (because of the short supply of piracetam), increasing the dose may lead to further benefit in some patients with PME. These results corroborate and extend those of previous clinical trials of piracetam in which more than 158 patients with myoclonus have been treated so far (**Table 4**). Efficacy and safety of piracetam treatment was previously evaluated in Europe and Japan, in short-term, open-label studies with daily doses ranging from 6 to 37 g for 2 and 24 weeks.^{4,5,7-9} In the 2 double-blind, placebo-controlled, crossover studies with piracetam as add-on therapy reported, the drug was given at a dose of 9.6 to 24 g/d for 2 weeks. In the first study, Brown et al⁶ observed significant improvement in motor performance during

treatment with piracetam compared with placebo in patients with cortical myoclonus. In the second study, Koskineniemi et al⁴ noted significant improvement in motor impairment with a dose-effect relationship, suggesting that a dose of 24 g/d could be highly beneficial. Most patients in our study achieved significant improvement in severity and frequency of myoclonus after the introduction of piracetam treatment, but the motor impairment index did not always reflect substantial clinical benefit. Motor performance in 3 patients remained purposeless and ataxic although less jerky, and this was partly correlated with the lack of improvement in functional ability for activities of daily living. This result is in contrast with previous observations, since both double-blind, placebo-controlled, open-label studies have shown significant improvement in functional disability.^{4-6,11} Most of our patients were at an advanced stage of PME and the disability was secondary not only to the myoclonus but also to pyramidal and cerebellar deficits. No significant clinical improvement in associated neurologic symptoms was noted.

Ataxic gait and dysarthria did not improve and this might be explained by the cerebellar origin of these signs. Two patients experienced dramatic reduction of seizure frequency during treatment with piracetam. In patients with PME repetitive myoclonic jerks frequently build up to a clonic-tonic-clonic-generalized seizure and it is likely that improvement in controlling myoclonic jerks helped suppress the initial phase of an attack of this type.

Table 1. Clinical Features of 11 Patients Treated With Piracetam*

Patient No.	Diagnosis	Duration of Disease, y	Clinical Features	Type of Imaging	Neurophysiology	Associated Treatment
1	Unverricht-Lundborg disease	8	GTCS + AM + RM + falls + anxiety and behavior disorder	MRI and MRS N	GEA + SWBA + giant SEPs	Valproate sodium + clonazepam
2	Unverricht-Lundborg disease	18	GTCS + AM + RM	MRI and MRS N	GEA + SWBA + giant SEPs	Valproate + clonazepam
3	Lafora disease	12	GTCS + AA + AM + RM + MD	MRI N	GEA + SWBA + giant SEPs	Valproate + clonazepam
4	Lafora disease	5	GTCS + AA + occipital seizures + AM + RM + MD	MRI N	GEA + SWBA	Valproate + clonazepam
5	Lafora disease	8	GTCS + AA + occipital seizures + AM + RM	MRI N	GEA + SWBA + giant SEPs	Valproate
6	Sialidosis type I	22	GTCS + AM + RM	MRI N	GEA + SWBA	Valproate + clonazepam + lamotrigine + phenobarbital
7	MERRF	18	GTCS + AM + RM + SS	MRI N	GEA + giant SEPs	Valproate
8	MERRF	11	GTCS + AM + RM + falls	MRI white matter changes and muscle MRS compatible with mitochondrial disease	GEA	Valproate
9	MERRF	19	GTCS + AM + RM	MRI white matter changes	GEA + SWBA	Lamotrigine + gabapentin
10	Undetermined	8	GTCS + AM + RM	MRI and MRS N + ¹⁸ F-DG-PET N	GEA	Ethosuximide + valproate
11	Undetermined	19	GTCS + AM + RM + MD	MRI and MRS N	GEA + SWBA	Valproate + clonazepam

*MERRF indicates mitochondrial encephalomyopathy with ragged red fibers; GTCS, generalized tonic-clonic seizures; AM, action myoclonus; RM, resting myoclonus; MRI, magnetic resonance imaging; MRS, magnetic resonance spectroscopy; N, normal; GEA, generalized epileptiform activity; SWBA, slow waves in background activity; SEPs, somatosensory evoked potentials; AA, atypical absence; MD, mental deterioration; SS, stimulus sensitivity; and ¹⁸F-DG-PET, fluorodeoxyglucose F 18-positron emission tomography.

Table 2. Summary of Method Used in Long-term Study to Score Myoclonus, Disability, and Associated Symptoms**A. Motor Impairment Index (range, 0-96)**

Resting myoclonus frequency scale: 0 to 32 (score 0-4 for each of 8 areas*)

Action myoclonus frequency scale: 0 to 32 (score 0-4 for stereotyped movement in each of 8 areas)

Action myoclonus severity scale: 0 to 32 (score 0-4 according to the degree of interference in activities of daily living for each of 8 areas)

B. Functional Disability (range, 0-28)

Score 0 to 4 for degree of impairment for: eating, swallowing, dressing, speech, hygiene, balance, and falling

C. Severity of Other Neurologic Symptoms (range, 0-18)

Seizure frequency (0-6)

Seizure severity (0-4)

Dysarthria (0-4)

Gait ataxia (0-4)

D1. Global impression of intensity of myoclonus by parents and the investigator (range, 0-4)

0 indicates none; 1, mild; 2, moderate; 3, marked; and 4, severe myoclonus causing great distress to the patient

D2. Global impression of the efficacy of the treatment by patient and the investigator

Marked indicates 75% to 100%; moderate, 50% to 74%; slight, 25% to 49%; no reduction, 0% to 24%; and worsening, <0%

Adjusted sum score = $[A/96 + B/28 + D/4] \times 10/3$

*Type, frequency, and severity of myoclonus evaluated, scoring for motor impairment assessed in 8 areas of the body: eyes, face, neck, trunk, and all 4 limbs.

High doses of piracetam were well tolerated and adverse effects were rare, mild, and transitory. They occurred early during treatment and did not require discontinuing the medication. Piracetam treatment was also well tolerated in larger series of patients with Alzheimer disease, although lower doses were generally used.¹⁷ The most common adverse effect was gastrointestinal discomfort, occurring in about one third of the patients.⁶ This is probably explained by the mild osmotic effect that piracetam may cause when high doses are

reached quickly. When giving 3.6 g at the beginning and increasing the dose gradually, none of the patients developed diarrhea.

To our knowledge, no long-term trials have been published to date and our report is the first open-label follow-up study of piracetam treatment in patients with myoclonus. The efficacy of piracetam treatment in long-term follow-up seemed to increase during the first year of treatment and then stabilized; this may be due to progression of the underlying disease.

Table 3. Effect of Piracetam in 11 Patients With Progressive Myoclonus Epilepsy During 18 Months of Treatment*

Test	Baseline	Duration of Piracetam Treatment, mo†				P‡
		1	6	12	18	
Adjusted sum score	7.8 (3.9-9)	6.4 (3.8-8.9) $P_1 = .008$	6.3 (3.6-8.8) $P_6 = .005$	6.1 (3.6-8.8) $P_{12} = .008$	6.1 (3.6-8.8) $P_{18} = .04$.003
Motor Impairment Index	65 (35-93)	54 (31-92) $P_1 = .002$	54 (27-88) $P_6 = .005$	54 (27-88) $P_{12} = .005$	56 (29-88) $P_{18} = .05$.001
Resting myoclonus frequency	20 (8-30)	18 (7-28) $P_1 = .008$	13 (2-26) $P_6 = .005$	12 (2-24) $P_{12} = .008$	12 (2-24) $P_{18} = .07$	<.0005
Action myoclonus frequency	28 (10-33)	21 (9-32) $P_1 = .003$	20 (6-30) $P_6 = .008$	20 (5-28) $P_{12} = .007$	22 (4-26) $P_{18} = .04$.0003
Action myoclonus severity	23 (11-32)	21 (9-32) $P_1 = .01$	17 (10-30) $P_6 = .01$	17 (6-25) $P_{12} = .01$	19 (4-22) $P_{18} = .07$.0001
Functional Disability	23 (5-27)	23 (4-27)	16 (4-24)	16 (4-24)	19 (4-25)	.06
Global assessment of intensity of myoclonus	7 (4-8)	6 (3-8) $P_1 = .02$	5 (3-8) $P_6 = .01$	5 (3-8) $P_{12} = .01$	5 (3-7) $P_{18} = .01$.001
Associated neurologic symptoms	13 (9-23)	13 (7-23)	13 (7-23)	13 (7-21)	12.5 (7-23)	.09
Seizure frequency and severity	5 (0-9)	4 (0-9)	5 (0-9)	4 (0-9)	4 (0-9)	.36

*All values are expressed as the median (range) scores of each scale.

† P_1 indicates the level of significance of the difference between baseline and the first month of treatment; P_6 , between baseline and the sixth month of treatment; P_{12} , between baseline and the 12th month of treatment; and P_{18} , between baseline and the 18th month of treatment.

‡ P indicates the level of significance of the difference between baseline and the entire period of treatment.

Table 4. Open-Label and Double-Blind Efficacy Studies of Piracetam in the Treatment of Myoclonus

Source, y	No. of Subjects	Diagnosis	Dose, g/d	Duration of Follow-up, wk	Effect of Myoclonus*
Obeso et al, ⁸ 1986	5	Different causes	6-9	2	Marked reduction in intensity and frequency
Obeso et al, ⁷ 1988	40	Different causes	18-24	1-3	Marked reduction in intensity and frequency
Remy and Genton, ⁹ 1991	4	Mediterranean myoclonus	12-37	24	Marked reduction in intensity and frequency
Guerrini et al, ¹⁰ 1996	5	Angelman syndrome	4.8-9.6	16	Significant effect on MII, FD, and IGA
Ikeda et al, ⁵ 1996	60	Different causes	12-21	4	Significant effect on MII, FD, SS, Hw, and IGA
Guerrini et al, ¹¹ 1998	3	Rett syndrome	300 mg/kg per day	12	Significant effect on MII, FD, and IGA
Brown et al, ⁶ 1993	21	Different causes	16.8	2	Significant effect on MII, FD, Hw, and IGA
Koskineniemi et al, ⁴ 1998	20	Progressive monoclous epilepsy	9.6-16.8-24	2	Significant effect on MII, FD, and IGA

**MI* indicates motor impairment index; *FD*, functional disability; *IGA*, investigator global assessment; *SS*, stimulus sensitivity; and *Hw*, handwriting.

The progression of disease in the group studied varied considerably with the causes.^{18,19} The worst prognosis was seen in Lafora disease that leads to relentless dementia. In patients with Unverricht-Lundborg disease or with mitochondrial encephalomyopathy with ragged red fibers the prognosis is slightly better but highly variable.²⁰

Though the prognosis in PME remains poor, progression is nowadays much slower and life expectancy better than in the past. Avoidance of phenytoin or other agents potentially causing ataxia may be a major factor.²¹ In our study the beneficial effect of piracetam treatment was long lasting and might suggest slowing progression of the underlying disease.

It is still unclear how piracetam treatment exerts its antimyoclonic effect. Its similarity to γ -aminobutyric acid (GABA) has suggested a GABAergic action, but it has been demonstrated that it does not act on any well-characterized receptor site and no interaction with known mechanisms involved in inhibitory and excitatory neurotransmission or membrane excitability has been shown.²²⁻²⁵ Piracetam is present in the polar heads of phospholipid membrane models and this interaction has been

shown to alter the physical properties of the cell membrane, increasing its fluidity.²³

It has been proposed that it could exert its antimyoclonic effect by potentiation of other antiepileptic drugs which in these conditions have been successfully used to control the seizures but not myoclonus.²² The best associated drugs were valproate and clonazepam both of which have antimyoclonic properties.^{26,27} Carbamazepine, phenytoin, lamotrigine, and vigabatrin have been shown to worsen myoclonus; hence, they should be avoided in the treatment of these disorders.^{28,29} Our patients receiving lamotrigine treatment were worse, but we were unable to draw a firm conclusion because of the few patients studied.

Piracetam given at high dosage in association with clonazepam and valproate is an effective and well-tolerated treatment of myoclonus in patients with PME. The favorable results reported here with piracetam treatment are long lasting, suggesting an improved prognosis and quality of life in patients with PME. Since most trials of piracetam treatment have been conducted in patients with advanced disease, longitudinal studies in naive patients are required to

further assess a possible effect on the natural history of these disorders.

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