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

Marco Fedi, MD; David Reutens, MD, FRACP; François Dubeau, MD, FRCP; Eva Andermann, MD, PhD, FCCMG; Daniela D’Agostino, MD; Frederick Andermann, MD, FRCP

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. 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. 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 al. 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 regardless of the underlying cause. 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 ± SD, 13.5 ± 7.2 g/d). Mean ± SD duration of treatment was 24.1 ± 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
PATIENTS AND METHODS

Eleven patients (8 males and 3 females; age range, 17-36 years; mean±SD age, 24.5±3.8 years) who had severe chronic disabling action and spontaneous myoclonus were treated with piracetam added to their previous drug regimens between November 1994 and November 1998. Before the introduction of piracetam treatment control of myoclonus was poor, despite the use of other antmyoclonic 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±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±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 ocipital 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 electrophysiologic 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 antmyoclonic 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.
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.

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.5,57 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 al observed significant improvement in motor performance during treatment with piracetam compared with placebo in patients with cortical myoclonus. In the second study, Koskiniemi et al 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 2

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Efficacy of Piracetam Treatment According to Investigator Observations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marked improvement</td>
<td>50% to 100% improvement in severity and frequency of myoclonus.</td>
</tr>
<tr>
<td>Moderate improvement</td>
<td>25% to 50% improvement in severity and frequency of myoclonus.</td>
</tr>
<tr>
<td>Slight</td>
<td>0% to 25% improvement in severity and frequency of myoclonus.</td>
</tr>
<tr>
<td>No change</td>
<td>0% to 25% worsening in severity and frequency of myoclonus.</td>
</tr>
<tr>
<td>Worsening</td>
<td>0% worse than the baseline.</td>
</tr>
</tbody>
</table>

Table 4

<table>
<thead>
<tr>
<th>Table 4</th>
<th>Detailed Scores of Myoclonus and Associated Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seizure frequency</td>
<td>Scored as follows: 0, no seizures; 1, less than 1 seizure weekly; 2, at least 1 seizure weekly; 3, at least 1 seizure monthly; 4, at least 1 seizure weekly; 5, at least 1, but less than 10 seizures daily; 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 follows: 0, none; 1, slight; 2, mild; 3, moderate; and 4, severe anarthria or imbalance.</td>
</tr>
<tr>
<td>Severity of other symptoms</td>
<td>Scored as: 0, no seizures; 1, slight; 2, mild; 3, moderate; and 4, severe anarthria or imbalance.</td>
</tr>
<tr>
<td>Global impression of intensity of myoclonus</td>
<td>Scored as: 0, none; 1, slight; 2, mild; 3, moderate; and 4, severe anarthria or imbalance.</td>
</tr>
<tr>
<td>Global impression of efficacy of treatment</td>
<td>Scored as: 0, none; 1, slight; 2, mild; 3, moderate; and 4, severe anarthria or imbalance.</td>
</tr>
</tbody>
</table>

This study demonstrates that piracetam is effective and well tolerated in the treatment of myoclonus.
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. The most common adverse effect was gastrointestinal discomfort, occurring in about one third of the patients. 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 1. Clinical Features of 11 Patients Treated With Piracetam

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Diagnosis</th>
<th>Duration of Disease, y</th>
<th>Clinical Features</th>
<th>Type of Imaging</th>
<th>Neurophysiology</th>
<th>Associated Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Unverricht-Lundborg disease</td>
<td>8</td>
<td>GTCS + AM + RM + falls + anxiety and behavior disorder</td>
<td>MRI and MRS N</td>
<td>GEA + SWBA + giant SEPs</td>
<td>Valproate sodium + clonazepam</td>
</tr>
<tr>
<td>2</td>
<td>Unverricht-Lundborg disease</td>
<td>18</td>
<td>GTCS + AM + RM</td>
<td>MRI and MRS N</td>
<td>GEA + SWBA + giant SEPs</td>
<td>Valproate + clonazepam</td>
</tr>
<tr>
<td>3</td>
<td>Lafora disease</td>
<td>12</td>
<td>GTCS + AA + AM + RM + MD</td>
<td>MRI N</td>
<td>GEA + SWBA + giant SEPs</td>
<td>Valproate + clonazepam</td>
</tr>
<tr>
<td>4</td>
<td>Lafora disease</td>
<td>5</td>
<td>GTCS + AA + occipital seizures + AM + RM + MD</td>
<td>MRI N</td>
<td>GEA + SWBA</td>
<td>Valproate + clonazepam</td>
</tr>
<tr>
<td>5</td>
<td>Lafora disease</td>
<td>8</td>
<td>GTCS + AA + occipital seizures + AM + RM</td>
<td>MRI N</td>
<td>GEA + SWBA + giant SEPs</td>
<td>Valproate</td>
</tr>
<tr>
<td>6</td>
<td>Sialidosis type I</td>
<td>22</td>
<td>GTCS + AM + RM</td>
<td>MRI N</td>
<td>GEA + SWBA</td>
<td>Valproate + clonazepam + lamotrigine + phenobarbital</td>
</tr>
<tr>
<td>7</td>
<td>MERRF</td>
<td>18</td>
<td>GTCS + AM + RM + SS</td>
<td>MRI N</td>
<td>GEA + giant SEPs</td>
<td>Valproate</td>
</tr>
<tr>
<td>8</td>
<td>MERRF</td>
<td>11</td>
<td>GTCS + AM + RM + falls</td>
<td>MRI N</td>
<td>GEA</td>
<td>Valproate</td>
</tr>
<tr>
<td>9</td>
<td>MERRF</td>
<td>19</td>
<td>GTCS + AM + RM</td>
<td>MRI N</td>
<td>GEA + SWBA</td>
<td>Lamotrigine + gabapentin</td>
</tr>
<tr>
<td>10</td>
<td>Undetermined</td>
<td>8</td>
<td>GTCS + AM + RM</td>
<td>MRI N and MRS N</td>
<td>GEA + SWBA</td>
<td>Valproate</td>
</tr>
<tr>
<td>11</td>
<td>Undetermined</td>
<td>19</td>
<td>GTCS + AM + RM + MD</td>
<td>MRI and MRS N</td>
<td>GEA + SWBA</td>
<td>Valproate + clonazepam</td>
</tr>
</tbody>
</table>

*MERRF indicates mitochondrial encephalopathy 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 18FDG-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]×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.
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 death from severe dementia. In patients with Unverricht-Lundborg disease or paroxysmal kinesigenic disorders, the prognosis is slightly better but highly variable.\(^{20}\)

Though the prognosis in PME remains poor, progression is nowadays much slower and life expectancy is 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 \(\gamma\)-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.\(^{22,23}\) 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.\(^{22,24}\) Carbamazepine, phenytoin, lamotrigine, and vigabatrin have been shown to worsen myoclonus; hence, they should be avoided in the treatment of these disorders.\(^{25,26}\) 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 show that the benefits are sustained.
further assess a possible effect on the natural history of these disorders.

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Piracetam was obtained on a compassionate basis from UCB Pharma, Brussels, Belgium.

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REFERENCES