Clinical Trial of Piracetam in Patients with Myoclonus: Nationwide Multiinstitution Study in Japan

Akio Ikeda, Hiroshi Shibasaki, †Kunio Tashiro, ‡Yoshikuni Mizuno, *Jun Kimura, and the Myoclonus/Piracetam Study Group

*Departments of Brain Pathophysiology and *Neurology, Kyoto University School of Medicine, Shogoin, Kyoto; †Department of Neurology, Hokkaido University School of Medicine, Hokkaido; and ‡Department of Neurology, Juntendo University School of Medicine, Tokyo, Japan*

Summary. Sixty patients with disabling myoclonus excluding mainly spinal myoclonus were treated by piracetam as an open-labeled study, and myoclonus score, neurological symptoms, functional disbility, and intensity of myoclonus were scored before and after treatment, including a blinded video inspection. Electrophysiological correlation also was investigated before and after treatment. Piracetam was effective in myoclonus, especially that of cortical origin, in both monotherapy and polytherapy. Piracetam also had positive benefits on gait ataxia and convulsions but not on dysarthria, and feeding and hand writing improved much more significantly. Psychologically significant improvement was seen in decreased motivation, sleep disturbance, attention deficit, and depression, all of which might be possibly secondary benefits associated with improvement of myoclonus. There was no positive correlation between clinical and electrophysiological improvement. Tolerance was good, and side effects were transient. However, hematological abnormalities observed in at least two patients in the present study should be kept in mind when relatively large doses of piracetam are administered, especially in combination with other antimyoclonic drugs. **Key Words:** Piracetam—Myoclonus—Progressive myoclonic epilepsy—Cortical myoclonus.

Myoclonus is described as a sudden, brief, shocklike involuntary movement occurring either spontaneously, in association with voluntary movements, or triggered by external stimuli. It is commonly seen in various neurological disorders such as anoxic, metabolic or toxic encephalopathy, lipidosis, heredogenerative disorders, and mitochondrial encephalomyopathy. It is often intractable to medical treatments. Clonazepam, primidone, valproic acid, and 5-hydroxytryptophan (5-HTP) may be insufficient in monotherapy or even in combination, and the side effects such as drowsiness and ataxia could further exaggerate the original symptoms seen in some kinds of patients (progressive myoclonic epilepsy syndrome, etc.), thus limiting their use.

Piracetam (2-oxo-1-pyrrolidineacetamide) has been used widely in Europe as a nootropic drug for the treatment of cognitive disorders and has few side effects (1,2). Since the first report by Terwinghe et al. (3), the effectiveness of piracetam on myoclonus has been increasingly recognized (4–9). Piracetam seems to be more effective on cortical myoclonus than on other types of myoclonus (8,9), but electrophysiological correlation with clinical improvement has been reported only in a few patients (7,8). In the present study, therefore, we conducted a multiinstitutional study of piracetam in a relatively large number of patients who demonstrated cortical myoclonus electrophysiologically, and the effects of piracetam on myoclonus, other accompanying symptoms, and electrophysiological findings were analyzed.

MATERIALS AND METHODS

This open-labeled treatment trial was performed according to the Guideline for Good Clinical Prac-

tice on Medical Products (10) based on the Helsinki II Declaration. The study also was approved by the committee in each individual institution shown in the Appendix.

Subjects

Patients with clinically disabling chronic myoclonus due to any etiology were accepted for this study. The presence of myoclonus, its severity, and the diagnosis of the underlying disorders were based on the judgment of certified neurologists in each institution. Patients were excluded if they were pregnant, <15 years of age, or had severe renal dysfunction. Patients with clear spinal myoclonus were also excluded from this study. All eligible patients (or their parent if necessary because of the patients' condition) gave written informed consent to participation in the study after understanding the objectives, methods, and potential risks associated with this trial.

Treatment Design and Its Pharmacokinetic Background

In the present study, piracetam, in a liquid formula with a 33% weight/volume content, was administered orally. To determine the maintenance dosage in each patient, a dosage finding trial was conducted during the initial 4–16 days as follows. Piracetam was administered initially at a dosage of 12 g/day, and the patients were observed for the following 4 days by the neurologist in charge as to whether the myoclonus improved. If it was judged to be noneffective, the dosage of piracetam was increased once every 4 days by 3 g/day each, up to the maximum of 24 g/day. When the initial dose was judged to have produced significant side effects or sufficient effects on myoclonus within the 4 days, then it was decreased by 3 g/day every 4 days, down to the minimum of 3 g/day.

The maintenance dose for each patient was continued for 4 weeks. If the patients were on other antimyoclonic or antiepileptic drugs before the trial, their dosage was maintained constant from at least 2 weeks before the beginning to the end of this trial.

In the present study, pharmacokinetics of piracetam also were studied for plasma levels and urinary excretion in selected patients after obtaining informed consent. The plasma level of piracetam was intermittently measured for 24 h in 10 patients after stopping the maintenance dose. In four patients with 15 g/day of maintenance dosage, peak plasma concentration (C_{max}), time to reach peak

plasma concentration (T_{max}), terminal half-life ($t\frac{1}{2}$), and the area under the plasma concentration curve (AUC) were 262.1 ± 146.1 μg/ml, 0.8 ± 0.3 h, 7.3 ± 4.8 h, and 2,456.7 ± 1,374.8 μg · hr/ml, respectively. Those parameters were 200.1 ± 88.1 μg/ml, 0.5 ± 0.0 h, 5.6 ± 1.2 h, and 1,674.3 ± 809.1 μg · h/ml, respectively, in three patients taking a maintenance dose of 18 g/day, and 281.4 ± 39.5 μg/ml, 0.8 ± 0.3 h, 5.3 ± 1.5 h, and 2,297.1 ± 799.7 μg · h/ml, respectively, in three patients taking 21 g/day. Daily urinary excretion of piracetam studied in 19 patients stayed constant between 60% and 100% of a total daily dose irrespective of the dosage. This finding suggests a rapid absorption and excretion of piracetam irrespective of the dosage. With regard to the analysis of plasma levels during maintenance treatment in 15 patients, the minimum plasma level of piracetam reached the steady state within 2 weeks. The minimum steady-state plasma level (C^{SS})min ranged from 42.7 ± 22.2 to 61.5 ± 48.7 μg/ml in seven patients taking 15 g/day, from 50.7 ± 43.2 to 63.1 ± 49.3 μg/ml in five patients with 18 g/day, and from 74.1 ± 24.0 to 96.1 ± 45.3 μg/ml in three patients with 21 g/day. These pharmacokinetic findings support the treatment design of the present study, i.e., three doses of piracetam a day and 4 weeks of maintenance treatment.

Patient Evaluation

Clinical Evaluation

The patients were examined by the certified neurologist in charge of each patient in each institution before entering the trial, during the dosage finding period, and at the end of the trial or when the treatment was terminated prematurely because of side effects or worsening of the clinical condition. Myoclonus was clinically scored with respect to the following four categories (resting myoclonus, stimulus-sensitive myoclonus, postural myoclonus, and action myoclonus). Myoclonus other than that of the postural type was scored for eight different body parts (eyes, face, neck, trunk, and four extremities) separately, and postural myoclonus was scored for each of the four extremities. For the frequency of resting myoclonus, each body area was scored from 0 to 4 degrees (absence of myoclonus being rated as 0, myoclonus occurring only during part of the day as 1, less frequent than once every 3 min as 2, once every 1–3 min as 3, and one occurring at least every minute as 4), and a total sum of the subscores was defined as the resting myoclonus

score (range 0–32). For the intensity of stimulus-sensitive myoclonus, score 1 was given for each part of the body for each response evoked by the five kinds of stimulus (loud noise, bright light, pinprick, tendon tap, and visual threat), and a total sum of the subscores was defined as the stimulus sensitivity score (range 0–40). For the frequency of postural myoclonus, each extremity was scored from 0 to 4 degrees (absence as 0, and postural myoclonus occurring in 1, 2, 3, and 4 out of 4 occasions of bed side examination as 1, 2, 3, and 4, respectively), and a total sum of the subscores was defined as the postural myoclonus frequency score (range 0–16). For the frequency of action myoclonus, each of eight body parts was scored from 0 to 4 degrees, similarly to that of the frequency of postural myoclonus, and a total sum of the subscores was defined as the action myoclonus frequency score (range 0–32). For the intensity of action myoclonus, eight body parts were scored from 0 to 4 degrees (absence as 0, and myoclonus that never, occasionally, frequently, and completely interfered with each corresponding function as 1, 2, 3, and 4, respectively), and a total sum of the subscores was defined as the action myoclonus severity score (range 0–32). Motor impairment score was then defined as the total sum of the resting myoclonus score, action myoclonus frequency score, and action myoclonus severity score (range 0–96). Global impression of the disability due to myoclonus was scored from 0 to 4 degrees (0 for absence of myoclonus, 1 for mild myoclonus without disturbance of daily activity, 2 for moderate myoclonus with some disturbance of daily activity, 3 for severe myoclonus with clear disturbance of daily activity, and 4 for marked myoclonus causing incapacity). This scoring was modified from the evaluation method of myoclonus previously described by other investigators (11).

In addition, the severity of neurological symptoms in close relation to myoclonus (generalized convulsions, ataxic gait and dysarthria) was given five grades (0, none; 1, slight; 2, mild; 3, moderate; 4, severe). The frequency of convulsion was also checked as "no," "yearly," "monthly," "weekly," and "daily" seizures, and it was taken into account for rating as described above. Disability in daily life was also scored in terms of the five functions (feeding, eating, dressing, hygiene, and hand writing) separately from 0 to 4 degrees. A total sum of the seven subscores consisting of these five scales and those of ataxic gait and dysarthria was defined as the functional disability score (range 0–28). Psycho-

logical state was rated by the nine items (sleep disturbance, decreased motivation, attention deficit, anxiety, depression, violence, emotional incontinence, memory disturbance, and abnormal behavior) using a five-grade scale (0, none; 1, slight; 2, mild; 3, moderate; 4, severe). Those examinations were conducted before entering the trial, at the time of starting maintenance dosage, and at the end of the trial or when treatment was terminated prematurely because of side effects or worsening of the clinical condition.

Video analysis of each patient also was made. The patient's state was recorded in each institution using a video camera in several conditions (conversation, forward arm stretching position, nose-finger-nose test, and standing and/or walking) on two occasions, i.e., before entering the trial and at the end of the trial, or when the treatment was terminated prematurely. The severity of myoclonus was scored (0–4 degrees) by the video-assessment committee, consisting of six certified neurologists without information of the date of recording by adopting the same evaluation scale as for the global impression of the disability shown above.

Electrophysiological Evaluation

Routine electroencephalography (EEG), somatosensory evoked potentials (SEPs) accompanied by long-loop reflex to median nerve electric stimulation, and jerk-locked back averaging (JLA) were performed before and at the end of the trial, and the presence or absence of epileptiform discharges, enhanced cortical SEPs, enhanced long-loop EMG responses, and cortical spikes preceding myoclonus were evaluated in each patient. These recording methods were modified from the ones published elsewhere (12,13) and were standardized across the institutions. SEPs were judged to be enlarged ("giant") when the amplitude of either P25 or N33 was more than the upper limits of normative values, which also were referenced elsewhere (12,13). Those examinations were conducted before entering the trial and at the end of the trial, or when the treatment was terminated prematurely.

Myoclonus of each patient was classified into cortical and subcortical type, based on the clinical and electrophysiological findings as follows. When EEG demonstrated epileptiform discharges clearly accompanying myoclonus and/or when giant SEPs, enhanced long-loop reflex, or cortical spikes demonstrated by JLA were present, then the myoclonus was judged to be of cortical origin. Otherwise, it

was judged to be either subcortical or undetermined depending on other findings, including clinical manifestations.

Subjective Evaluation

The patients' self assessment of their own myoclonus was scored from 0 to 4 degrees (absence of jerk as 0, slight 1, mild 2, moderate 3, and severe 4). It was evaluated before entering the trial, when starting maintenance dosage, and at the end of the trial, or when the treatment was terminated prematurely.

Methods for Evaluating Safety of the Treatment

Physical examination, urinalysis, complete blood cell count, electrolytes, blood glucose, and liver function tests were conducted before entering the trial and at the end of the trial.

Evaluation of Efficacy and Statistical Methodology

Statistical analyses were performed on an intention-to-treat basis that included all patients who entered the present open-labeled study. The stimulus sensitivity score, resting myoclonus score, action myoclonus frequency score, action myoclonus severity score, postural myoclonus score, and functional disability score evaluated before the trial were compared with those evaluated at the end of the trial by paired t test. The scores of subjective evaluation, global impression of the disability, and video analysis also were compared between those two occasions by the Wilcoxon two-sample sign-rank test. All tests were two tailed, and the level of significance accepted was 5%. In addition, the myoclonus index score was defined, by using the seven scores or rates as described above, as [(stimulus sensitivity score/40) + (postural myoclonus frequency score/16) + (motor impairment score/96) + (functional disability score/28) + (global impression of the disability/4) + (video analysis/4) + (subjective evaluation/4)] × 10/7, and was compared between those two occasions by paired t test.

RESULTS

Demographic Data

From July 1992 to October 1994, 60 patients (31 men and 29 women; age range 15–74 years, mean 43.4) were enrolled. Duration of disease ranged from 2 months to 50 years (mean 13.7 years). With regard to the degree of disability in daily life due to the presence of myoclonus, 31 patients (51.7%) were independent essentially without assistance, 14

(23.3%) were independent but needed some assistance, eight (13.3%) were dependent on significant assistance, and seven (11.7%) were completely bedridden. Thirty-four patients (56.7%) were categorized as having the so-called progressive myoclonic epilepsy syndrome (Table 1). Maintenance dosage of piracetam ranged from 9 to 24 g/day (median 18). Forty-nine of 60 patients were on other antimyoclonic drugs: monopharmacy in 15 patients (clonazepam in 11, valproic acid in three, and carbamazepine in one) and polypharmacy in 34 (clonazepam + valproic acid in 10, clonazepam + valproic acid + primidone in four, clonazepam + valproic acid + phenobarbital in two, clonazepam + valproic acid + diazepam in two, clonazepam + valproic acid + zonisamide in two, and various combinations in the other 13).

Myoclonus also was classified into cortical (37 patients, 61.7%) and subcortical (six patients, 10.0%) type, and in 17 patients (28.3%) the type was undetermined. For final analysis of efficacy of piracetam on myoclonus, seven of the 60 patients were excluded for the following reasons: two patients were too ill in general to perform global assessment of myoclonus, and five were judged to have involuntary movements other than myoclonus by the video-assessment committee.

Effects of Piracetam

In the overall 53 patients, piracetam was judged to be effective on myoclonus in terms of all scores of subjective evaluation ($p < 0.0001$), stimulus sensitivity ($p < 0.01$), resting myoclonus ($p < 0.001$), postural myoclonus frequency ($p < 0.0001$), action myoclonus frequency ($p < 0.0001$), action myoclonus severity ($p < 0.0001$), global impression of the

TABLE 1. *Clinical diagnosis of 60 patients*

Progressive myoclonic epilepsy syndrome	34
Sialidosis	10
Mitochondrial encephalopathy	3
Familial myoclonus and epilepsy (19,20)	2
Dentato-rubro-pallido-luysian atrophy	1
Lafora's disease	1
Ramsay Hunt syndrome	1
Others	16
Anoxic encephalopathy	5
Essential myoclonus	4
Slow viral infection	3
Alzheimer's disease	2
Chronic brainstem encephalitis	1
Segmental myoclonus	3
Spinal myoclonus	1
Others	7

disability (p < 0.0001), and video analysis (p < 0.0001). Functional disability score at the end of the trial also was significantly improved from the baseline score before the beginning of the treatment (p < 0.0001). Feeding (p < 0.001) and hand writing (P < 0.001) were more significantly improved than dressing (p < 0.01) and hygiene (p < 0.01). No significant change was observed in eating (Table 2).

Among neurological symptoms, no, slight, mild, moderate, and severe generalized convulsions were seen in 79.2%, 1.9%, 9.4%, 7.5%, and 1.9%, respectively, of all patients before the trial, and in 88.7%, 5.7%, 5.7%, 0%, and 0%, respectively, after the end of the trial (p < 0.01). Similarly, no, slight, mild, moderate, and severe ataxic gait was initially seen in 30.8%, 13.5%, 19.2%, 17.3%, and 19.2%, respectively, of the patients before the trial, and it was seen in 36.5%, 21.2%, 17.3%, 15.4%, and 9.6%, respectively, after the trial (p < 0.0001). Dysarthria also improved, although less significantly (p < 0.05).

With regard to the change in psychological states, only a small number of patients had these symptoms before the trial (Fig. 1). Significant improvement was seen in decreased motivation (p < 0.001), sleep disturbance (p < 0.01), attention deficit (p < 0.05), and depression (p < 0.05), but other parameters showed no significant changes. Worsening of the symptoms was seen only in one patient with Lafora's disease in the parameter of "violence." It was finally undetermined as to whether it was caused by piracetam or occurred as one of the symptoms of the underlying progressive disorder.

Five patients had the maintenance dosage of piracetam of ≤12 g (12-g group), 12 patients had that of 15 g (15-g group), 15 patients 18 g (18-g group), and 19 patients ≥21 g (21-g group). The myoclonus index score was not significantly improved in the

12-g group, but was significantly improved in the 15-g group (p < 0.01), 18-g group (p < 0.001), and 21-g group (p < 0.001).

Comparing the patient group having cortical myoclonus with the remaining groups (patients with myoclonus of either subcortical origin or undetermined type), the myoclonus index score was more significantly improved in the cortical myoclonus group (p < 0.0001) than in the other groups (p < 0.01). No significant change in the myoclonus index score was seen with respect to other parameters (age, degree of daily life disability, and duration of disease). Piracetam was similarly effective in both patient groups with and without other antimyoclonic drugs.

Effects of Piracetam in Patients with Cortical Myoclonus

In 35 patients with cortical myoclonus, piracetam was judged to be effective on myoclonus in terms of all scores of subjective evaluation (p < 0.0001), stimulus sensitivity (p < 0.05), resting myoclonus (p < 0.01), postural myoclonus (p < 0.0001), action myoclonus frequency (p < 0.0001), action myoclonus severity (p < 0.001), global impression of the disability (p < 0.0001), and video analysis (p < 0.001). Functional disability score was also significantly improved from before the beginning to the end of the trial (p < 0.001), and feeding (p < 0.001) was more significantly improved than dressing (p < 0.01), hand writing (p < 0.01), or hygiene (p < 0.05), whereas no significant change was observed in eating (Table 3).

Among neurological symptoms, no, slight, mild, moderate, and severe generalized convulsions were seen in 80.0%, 2.9%, 5.7%, 8.6%, and 2.9%, respectively, of all patients before the trial, and in 88.6%, 8.6%, 2.9%, 0%, and 0%, respectively, after the

TABLE 2. *Effects of piracetam*

| Score	Before trial[a]	End of trial[a]	p
Myoclonus			
Subjective evaluation	3.0 ± 0.8	2.1 ± 1.1	<0.0001
Stimulus sensitivity	3.3 ± 5.8	1.6 ± 3.0	<0.01
Resting myoclonus	7.6 ± 7.8	4.7 ± 5.8	<0.001
Postural myoclonus frequency	8.6 ± 5.1	6.5 ± 5.1	<0.001
Action myoclonus frequency	15.5 ± 8.5	11.4 ± 8.4	<0.0001
Action myoclonus severity	12.7 ± 7.2	9.9 ± 7.0	<0.0001
Global impression of the disability	2.8 ± 0.8	2.3 ± 1.0	<0.0001
Video analysis	2.7 ± 0.9	2.2 ± 1.0	<0.0001
Myoclonus index score	4.9 ± 1.5	3.8 ± 1.7	<0.0001
Functional disability score	9.7 ± 6.6	8.2 ± 6.6	<0.0001

[a] Values are means ± SD.
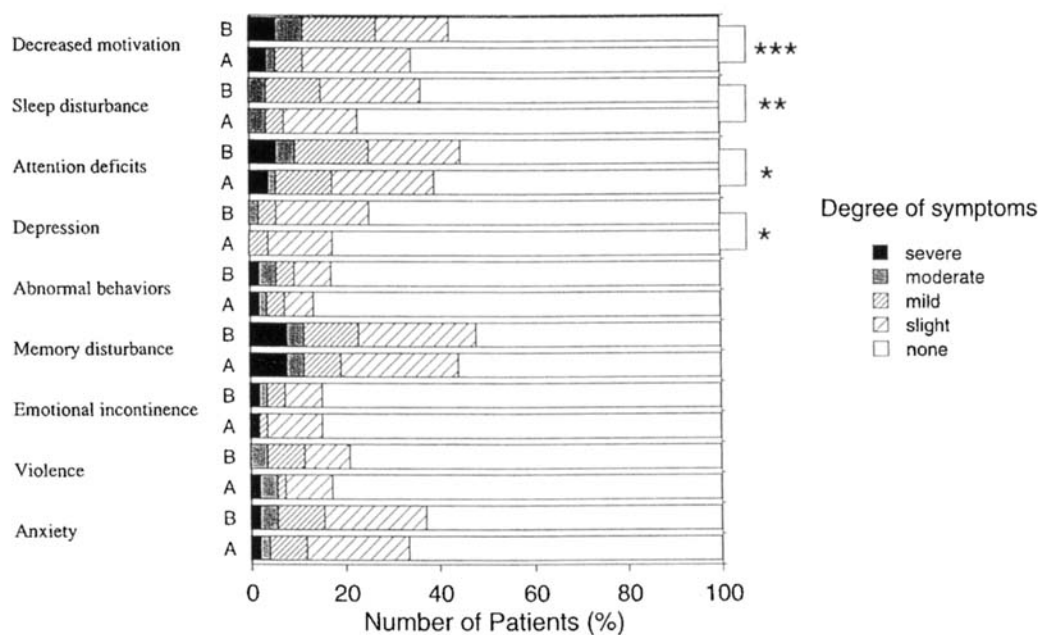
FIG. 1. The change of psychological states (sleep disturbance, decreased motivation, attention deficit, anxiety, depression, violence, emotional incontinence, memory disturbance and abnormal behavior) before and after the treatment. B, before treatment; A, after treatment. ***p < 0.001, **p < 0.01, *p < 0.05.

treatment (p < 0.05). Similarly, no, slight, mild, moderate, and severe ataxic gait was initially seen in 32.4%, 11.8%, 26.5%, 14.7%, and 14.7%, respectively, of the patients before the trial, and it was seen in 41.2%, 20.6%, 23.5%, 11.8%, and 2.9%, respectively, after the treatment (p < 0.001). Dysarthria was not significantly improved. As regards the nine psychological symptoms as described above, significant improvement was seen in decreased motivation (p < 0.01), sleep disturbance (p < 0.01), and attention deficit (p < 0.05), but other parameters showed no significant changes.

The number of patients with maintenance dosage of piracetam of ≤12 g (12-g group), 15 g (15-g group), 18 g (18-g group), and ≥21 g (21-g group)

were 3, 9, 13, and 9, respectively. The myoclonus index score was significantly improved in all groups; the 12-g group' (p < 0.05), 15-g group (p < 0.01), 18-g group (p < 0.001), and 21-g group (p < 0.01). With regard to other parameters (age, degree of daily life disability, and duration of disease), no significant change in myoclonus index score was seen.

Effects of Piracetam in Patients with Progressive Myoclonic Epilepsy

In 34 patients with progressive myoclonic epilepsy, piracetam was judged to be effective on myoclonus in terms of all scores of subjective evaluation (p < 0.0001), stimulus sensitivity (p < 0.05),

TABLE 3. *Effects of piracetam in patients with cortical myoclonus*

Score	Before trial[a]	End of trial[a]	p
Myoclonus			
Subjective evaluation	2.9 ± 0.9	1.8 ± 1.0	<0.0001
Stimulus sensitivity	3.3 ± 5.5	1.5 ± 2.9	<0.05
Resting myoclonus	7.0 ± 7.3	4.0 ± 4.9	<0.01
Postural myoclonus frequency	8.8 ± 4.6	6.3 ± 4.8	<0.0001
Action myoclonus frequency	15.2 ± 9.0	10.7 ± 8.5	<0.0001
Action myoclonus severity	11.5 ± 7.1	8.3 ± 6.0	<0.001
Global impression of the disability	2.5 ± 0.8	1.9 ± 0.7	<0.0001
Video analysis	2.5 ± 0.9	1.9 ± 0.9	<0.001
Myoclonus index score	4.7 ± 1.6	3.3 ± 1.5	<0.0001
Functional disability score	8.7 ± 6.4	6.7 ± 5.9	<0.001

[a] Values are means ± SD.

resting myoclonus (p < 0.001), postural myoclonus (p < 0.005), action myoclonus frequency (p < 0.0001), action myoclonus severity (p < 0.001), global impression of the disability (p < 0.0001), and video analysis (p < 0.001). Functional disability score also was significantly improved from before the beginning to the end of the trial (p < 0.001), and feeding (p < 0.01) and hand writing (p < 0.01) were more significantly improved than dressing (p < 0.05), whereas no significant change was observed in eating and hygiene (Table 4).

Among neurological symptoms, no, slight, mild, moderate, and severe generalized convulsions were seen in 76.5%, 2.9%, 8.8%, 8.8%, and 2.9%, respectively, of all patients before the trial, and in 85.3%, 8.8%, 5.9%, 0%, and 0%, respectively, after the treatment (p < 0.05). Similarly, no, slight, mild, moderate, and severe ataxic gait was initially seen in 27.3%, 15.2%, 21.2%, 18.2%, and 18.2%, respectively, of the patients before the trial, and it was seen in 33.3%, 24.2%, 21.2%, 18.2%, and 3.0%, respectively, after the treatment (p < 0.001). Dysarthria was not significantly improved. As regards the nine psychological symptoms as described above, significant improvement was seen only in decreased motivation (p < 0.05).

Electrophysiological Findings

Cortical SEPs were recorded in 30 patients both before and after the trial, and the amplitude of P25 obtained on the two occasions was compared by paired t test. In 16 patients in whom the median nerve on each side was stimulated, the side with larger amplitude taken before the trial was chosen for analysis. The mean amplitude of P25 among those 30 patients was 17.0 ± 11.9 μV before and 13.8 ± 7.8 μV after the trial, and the difference was not significant. Four patients who showed improve-

ment in myoclonus index score had a larger P25 amplitude after the trial than before. In 29 patients with cortical myoclonus, the mean amplitude of P25 was 17.3 ± 12.0 μV before and 14.0 ± 7.8 μV after the trial, and there was again no significant difference between the two. The correlation coefficient between the percentage difference of the myoclonus index obtained before and after the trial, and that of the amplitude of P25 measured before and after the trial was 0.235 in all patient group, 0.37 in patients with progressive myoclonic epilepsy, and 0.23 in patients with cortical myoclonus.

Side Effects

Piracetam was relatively well tolerated, but complaints judged to be side effects related to piracetam were recorded on 21 occasions in 13 patients (24.5%) (Table 5). Most of them were related to the symptoms of the alimentary tract. All these symptoms occurred during the initial dose-finding period, with the dosage between 9 and 18 g. Therefore, there was no positive relationship between the dosage and the occurrence of these symptoms. Generalized seizure occurred just after the trial only in one patient, who had a history of generalized seizures occurring every several months before entering this trial.

One patient had thrombocytopenia and leukopenia, and two other patients had leukopenia (trough levels of 2,300 counts/μl and 3,800/μl). The former patient, a 28-year-old woman with progressive myoclonic epilepsy, was also on clonazepam (4 mg/day), phenobarbital (180 mg/day), and diazepam (8 mg/day). Leukocyte and platelet count decreased down to 1,800/μl and 90,000/μl, respectively, which recovered immediately after stopping piracetam. With regard to the latter two patients, both of whom were also on other antimyoclonic drugs, leukopenia

TABLE 4. *Effects of piracetam in patients with progressive myoclonic epilepsy*

Score	Before trial[a]	End of trial[a]	p
Myoclonus			
Subjective evaluation	2.9 ± 0.9	2.0 ± 1.0	<0.0001
Stimulus sensitivity	3.9 ± 6.7	1.7 ± 3.1	<0.05
Resting myoclonus	7.1 ± 7.4	4.5 ± 6.0	<0.001
Postural myoclonus frequency	8.3 ± 5.3	6.5 ± 4.8	<0.005
Action myoclonus frequency	15.9 ± 8.9	12.3 ± 8.1	<0.0001
Action myoclonus severity	12.9 ± 7.5	10.3 ± 6.4	<0.001
Global impression of the disability	2.6 ± 0.8	2.2 ± 0.8	<0.0001
Video analysis	2.6 ± 0.8	2.1 ± 1.0	<0.001
Myoclonus index score	4.8 ± 1.5	3.7 ± 1.5	<0.0001
Functional disability score	8.9 ± 6.2	7.1 ± 5.6	<0.001

[a] Values are means ± SD.

TABLE 5. *Side effects noted during trial*

Complaints	No. of patients
Gastric discomforts	6
Diarrhea	5
Sleepiness	2
Seizure	1
General fatigue	1
Others	8

recovered when the dosage of other antimyoclonic drugs was decreased in one patient, and leukopenia remained the same (3,800/μl) without any clinical symptom even after stopping piracetam in the other patient.

DISCUSSION

The present study showed that piracetam was effective and useful for controlling myoclonus of both cortical and subcortical origin. In patients with myoclonus of cortical origin that was electrophysiologically proven, the improvement was much more significant. With regard to accompanying neurological symptoms, gait ataxia and convulsions improved with piracetam, but dysarthria did not. In fact, gait could be disturbed by not only ataxia but also action myoclonus, and it is often difficult to judge which of them is the main cause of the gait ataxia or gait disturbance. Therefore it is likely that decreased myoclonus apparently improved gait ataxia clinically and that cerebellar ataxia itself might not necessarily have changed. On the other hand, because dysarthria represents predominantly a cerebellar symptom, it did not change with the treatment. Convulsions are often seen in patients with progressive myoclonic epilepsy occurring as myoclonic seizures, and it seems that piracetam decreased the number of epileptic seizures in the present study. An antiepileptic effect of piracetam has not been clearly pointed out previously, but a crossover trial of piracetam for patients with cortical myoclonus showed that more epileptic attacks occurred during the placebo phase than during the piracetam phase (9). This suggests the possibility of withdrawal seizures, supporting a role of piracetam in suppressing epileptic activity. The improvement of myoclonus possibly avoids the initial phase of myoclonic seizures that leads to myoclonic- (or clonic-) tonic-clonic seizures. From the psychological point of view, significant improvement was seen in decreased motivation, sleep disturbance, attention deficit, and depression. These effects may be ex-

plained in part by secondary benefits in association with clinical improvement of myoclonus.

Electrophysiologically, the amplitude of P25 of the median nerve SEPs tended to become smaller on the treatment, but this did not reach statistical significance. Moreover, at least four patients who obtained improvement in myoclonus from the treatment had an even larger amplitude P25 after the treatment than before. Obeso et al. (8) described at least two patients who showed a marked reduction in the size of giant SEPs by piracetam, whereas they did not show any clinical improvement. This is also consistent with the previous clinical observation that giant SEPs do not necessarily improve with other antimyoclonic drugs, even when the myoclonus clinically improves significantly (14). Therefore, it is likely that the effect of piracetam on myoclonus is not necessarily mediated through the mechanism by which cortical SEPs are enhanced.

The mechanism by which piracetam suppresses mainly cortical myoclonus is still unclear. It is unlikely that piracetam acts by enhancing plasma levels of other antimyoclonic drugs because piracetam was as effective as monotherapy, as shown in the present and previous studies, and also because no change in the plasma levels of at least valproic acid or primidone was reported when piracetam was taken as part of polytherapy (7–9). Previous studies failed to demonstrate that piracetam modifies brain levels of several neurotransmitters (dopamine, serotonin, and γ-aminobutyric acid) (15), which have been proven to be involved in the generation of cortical myoclonus and accompanying enhanced cortical SEPs (16,17). Piracetam, as a nootropic drug, stimulates cerebral acetylcholine synthesis and release (2). Although central cholinergic modulation by piracetam has positive effects on learning and memory in dementia patients with Alzheimer's disease (1), it is uncertain as to whether the cholinergic mechanism also plays some role in the generation or suppression of myoclonus. It might be worthwhile mentioning that some patients with Alzheimer's disease have both dementia and myoclonus of cortical origin. In the present study, two patients (67 and 56 years of age) with Alzheimer's disease showed a mild improvement of myoclonus with piracetam. This might suggest that both myoclonus and dementia seen at least in the two patients share common pathophysiological mechanisms. A further study is needed to explore this hypothesis.

Gastric discomforts and diarrhea were reported as side effects in the present study. Piracetam has

been known to be quite safe in terms of side effects throughout its long history as a nootropic drug among European countries (2). Gastric discomforts commonly have been reported, occurring in about one third of the patients (8). Diarrhea, although transient only during the initial period, was more frequently seen in the present study than in previous reports (7,9). This could be attributed to the fact that in the present study piracetam was taken by mouth in a sweet solution that irritates bowel movements initially. In addition, both thrombocytopenia and leukopenia, and mild leukopenia were reported in one and two patients, respectively. All of them were also on other antimyoclonic drugs. In at least one of the three patients, these hematological abnormalities became normal after decreasing the dosage of the concomitant antimyoclonic drugs. These side effects were not reported previously in patients taking piracetam for myoclonus (7–9) or in patients with dementia (1). The trials for myoclonus, including the present study, have used larger doses (9–24 g/day) than used in patients with dementia (2.4–4.8 g/day) (18). Therefore, the hematological disturbances observed in the present study should be kept in mind as one of the potential dose-dependent side effects when a large dose of piracetam is administered, especially in combination with other antimyoclonic drugs.

We conclude that piracetam is useful to control myoclonus, especially that of cortical origin. It is well tolerated with only mild alimentary tract symptoms. Because clinical improvement was not necessarily correlated with a decrease in amplitude of cortical SEPs, and because the degree of myoclonus improvement varied among patients with cortical myoclonus, the mechanism underlying the myoclonus suppression by piracetam requires further study.

APPENDIX

The following persons and institutions participated in the Myoclonus/Piracetam Study Group. Principal investigator: Hiroshi Shibasaki. Coordinators: Jun Kimura, Kunio Tashiro, and Yoshikuni Mizuno. Participating institutions: Hokkaido University Hospital, Iwate Medical School Hospital, Yamagata University Hospital, Tohoku University Hospital, Fukushima Medical School Hospital, Tsukuba University Hospital, Niigata University Hospital, Jichi Medical School Hospital, Gunma University Hospital, Juntendo University Hospital, Tokyo University Hospital, Tokyo Metropolitan Neurological Hospital, Tokyo Medical and Dental University Hospital, National Center of Neurology and Psychiatry Musashi Hospital, Kanazawa University Hospital, Kanazawa Medical School Hospital, Kyoto University Hospital, National Cardiovascular Center, Osaka University Hospital, Kansai Medical School Hospital, Kawasaki Medical School Hospital, Yamaguchi University Hospital, Matsuyama Red-Cross Hospital, Occupational and Environmental Health University Hospital, Kyushu University Hospital, Saga Medical School Hospital, Nagasaki University Hospital, Kumamoto University Hospital, Ohita Medical School Hospital, Miyazaki Medical School Hospital, and Kagoshima University Hospital. Video-assessment committee: Akio Ikeda, Jun Kimura, Nobuo Kohara, Yoshikuni Mizuno, Hiroshi Shibasaki, and Kunio Tashiro. Biostatistical analysis: Wataru Kashiwagi, Hiroshi Ichikawa, and Akemi Sakuragi. Coordinator at Taiho Pharmaceutical Company: Yutsuru Urano.

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