Movement Disorders
Vol. 8, No. 1, 1993, pp. 63–68

Effectiveness of Piracetam in Cortical Myoclonus

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Summary: Twenty-one patients with disabling spontaneous, reflex, or action myoclonus due to various causes, who had shown apparent clinical improvement on introduction of piracetam, entered a placebo-controlled double-blind crossover trial of piracetam (2.4–16.8 g daily). All but one patient had electrophysiological evidence of cortical myoclonus. Patients were randomly allocated to a 14-day course of piracetam followed by identical placebo, or placebo followed by piracetam. Nineteen patients received piracetam/placebo in addition to their routine antimyoclonic treatment (carbamazepine, clonazepam, phenytoin, primidone, sodium valproate, or tryptophan plus isocarboxazid, alone or in combination) and two received piracetam/placebo as monotherapy. All patients were rated at the end of each treatment phase using stimulus sensitivity, motor, writing, functional disability, global assessment, and visual analogue scales. Ten of the 21 patients had to be rescued from the placebo phase of the trial because of a severe and intolerable exacerbation of their myoclonus. No patients required rescue from the piracetam phase of the double-blind trial. When the 21 patients were considered together, there was a significant improvement in motor, writing, functional disability, global assessment, and visual analogue scores during treatment with piracetam compared with placebo. The total rating score also improved significantly with piracetam, by a median of 22%. Piracetam, usually in combination with other antimyoclonic drugs, is a useful treatment for myoclonus of cortical origin. **Key Words:** Piracetam—Cortical myoclonus.

The treatment of myoclonus can be difficult (1,2). 5-Hydroxytryptophan plus carbidopa, clonazepam, sodium valproate, or primidone may be inadequate in monotherapy or in combination (2), and side effects such as drowsiness and ataxia may limit their use. Piracetam (2-oxo-1-pyrrolidineacetamide) has been widely used in some European countries for the treatment of cognitive disorders, and has few side effects. In 1978 Terwinghe et al. (3) reported a dramatic improvement in a patient with postanoxic action myoclonus during treatment with piracetam. Since then several case reports (4–6) and two open-label trials (7,8) have suggested that piracetam may be effective in myoclonus. In an open assessment of piracetam in 40 patients with different clinical and electrophysiological types of myoclonus, Obeso et al. (8) concluded that piracetam was only effective in myoclonus of cortical origin, and was of value only in combination with other antimyoclonic medication. In this article we report the first crossover, double-blind, placebo-controlled trial of piracetam in myoclonus and establish that piracetam is an effective treatment of cortical myoclonus.

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METHODS

In the study patients, who were thought to have responded to piracetam treatment in an open-label study, were challenged later in a placebo-controlled double-blind, crossover trial. The study was com-

pleted during 2 years and involved a single neurological center.

Patients

Twenty-four patients entered the run-in phase of the study, and 21 (8 male and 13 female; median age 33 years, range 21–72 years) went on to enter the placebo-controlled, double-blind, crossover study. One patient dropped out before the controlled phase because of an adverse event (suspected pulmonary embolus). Two other patients failed to respond to piracetam in the run-in phase and did not enter the controlled phase of the trial. All the patients had been stable on fixed treatment for at least 1 month. All but one had electrophysiological evidence of cortical myoclonus; this consisted of either the presence of a short-latency timelocked cortical correlate preceding myoclonic jerks on backaveraging (n = 10), or the combination of the latter with giant cortical sensory-evoked potentials (n = 10). The remaining patient had postanoxic myoclonus, which clinically was compatible with a cortical origin, but could not be studied electrophysiologically.

All 21 patients had action myoclonus; 9 of these had spontaneous myoclonus and 9 of these also had stimulus-sensitive myoclonus. Eight patients had a static postanoxic encephalopathy, seven had progressive myoclonic ataxia of unknown etiology (despite extensive investigation), three had progressive myoclonic epilepsy of unknown etiology (despite extensive investigation), and one patient each had Huntington's disease, myoclonus in association with coeliac disease, and epilepsia partialis continua of unknown etiology.

Informed consent according to the Helsinki II declaration was obtained from all patients. The study was approved by the local ethical committee.

Treatment

In the run-in phase, piracetam was administered open label in increasing dosage, initially 7.2 g/day (with the exception of one patient who responded to 2.4 g/day), increased by 4.8 g/day every 3–4 days, up to a maximum of 16.8 g/day, or until stable clinical benefit was evident. The 21 patients who entered the placebo-controlled, double-blind, crossover trial were thought to have derived benefit from piracetam (median dosage 16.8 g/day, range 2.4–16.8 g/day) in the run-in phase of the study. Nineteen of these 21 patients were taking other antimyoclonic drugs (Table 1). These were continued unchanged throughout the trial.

During the placebo-controlled, double-blind, crossover trial, patients received either piracetam (median dosage 16.8 g/day, range 2.4–16.8 g/day) followed by placebo (10 patients), or placebo followed by piracetam (11 patients), according to a computer-generated randomization schedule. There was no washout period between each course of treatment. The piracetam and placebo tablets could not be distinguished by size, shape, color, smell, or taste. The dosages of other antimyoclonic or antiepileptic drugs were maintained constant during the trial period. The median duration of the course of piracetam was 14 (range 9–15) days. The median

TABLE 1. *Drug treatment in the 21 patients*

	No. of patients	Maximum daily dose for each drug
Monotherapy		
Piracetam	2	16.8 g
Bitherapy		
Piracetam + sodium valproate	2	16.8 g/2 g
Piracetam + clonazepam	1	16.8 g/2 mg
Polytherapy		
Piracetam + clonazepam + sodium valproate	6	16.8 g/4 mg/2.2 g
Piracetam + clonazepam + carbamazepine	1	7.2 g/12 mg/1 g
Piracetam + clonazepam + phenytoin	1	12 g/5 mg/340 mg
Piracetam + clonazepam + primidone	1	16.8 g/4 mg/625 mg
Piracetam + clonazepam + carbamazepine + sodium valproate	2	16.8 g/6 mg/700 mg/2 g
Piracetam + clonazepam + clobazam + sodium valproate	1	12 g/16 mg/20 mg/3 g
Piracetam + clonazepam + primidone + sodium valproate	1	16.8 g/6 mg/750 mg/1 g
Piracetam + clonazepam + tryptophan[a] + sodium valproate	2	12 g/6 mg/6 g/1.6 g
Piracetam + clonazepam + carbamazepine + primidone + sodium valproate	1	16.8 g/3 mg/800 mg/250 mg/3 g

During the placebo-controlled, double-blind, crossover trial, piracetam was replaced by trial medication (i.e, placebo or piracetam in identical tablets), while other treatments were continued unchanged.

[a] Tryptophan was prescribed with isocarboxacid 40 mg daily.

duration of treatment with placebo was only 9 (range 1–24) days, because 10 patients were prematurely withdrawn from this phase due to a severe and intolerable exacerbation of their myoclonus.

Clinical Examinations

Each patient was examined by the same "blind" neurologist at the end of each planned course of treatment, or when a treatment course had to be terminated prematurely to rescue individuals whose symptoms worsened intolerably.

Patients were scored on six rating scales (stimulus sensitivity, motor impairment, functional disability, global impression, handwriting, and visual analogue scales). The total score, consisting of the sum of the six individual test scores, was also calculated. Stimulus sensitivity, motor impairment, functional disability, and a global impression of disability were scored using a modification of the rating scales described by Truong and Fahn (9).

In the rating scales for stimulus sensitivity and motor impairment, the body was divided into the following eight areas: eyes, face, neck, trunk, right and left arm, and right and left leg. In assessing stimulus sensitivity, a score of 1 point was given for each body area involved in the reflex response to a tendon tap to a finger and toe. A pinprick to a finger and toe, loud noise from a handclap, flash of bright light, and visual threat of a hand thrust before the face were similarly scored. These scores were summed to give the stimulus sensitivity score. The motor impairment score consisted of the sum of three subscores: the spontaneous myoclonus score, the action myoclonus frequency score, and the action myoclonus severity score. In assessing spontaneous myoclonus, each body area was scored as follows: 0 for no spontaneous myoclonus and 1, 2, 3, and 4 for spontaneous myoclonus occurring only during part of the day, less frequently than every 3 min, every 1–3 min, or at least every minute, respectively. In assessing the frequency and severity of action myoclonus, the patient was asked to repeat four times a stereotyped movement involving each body area. The frequency of the action myoclonus was then rated as follows: 0 for no myoclonus, and 1, 2, 3, and 4 for action myoclonus occurring in 1 of 4, 2 of 4, 3 of 4, or in all 4 of the movements, respectively. The scores for each of the body areas were then summed to give the action myoclonus frequency score. The severity of the action myoclonus was rated for each body area during the performance of the stereotyped movements as follows: 0 for no myoclonus, and 1, 2, 3, and 4 for myoclonus that never, occasionally, frequently, and completely interfered with function, respectively. The action myoclonus severity score was the sum of the scores for each body area.

In assessing functional disability, speech, swallowing, eating (the ability to use a knife and fork), washing, dressing, and walking were each rated on a scale of 0–4 (normal being rated as 0, and anarthria, marked dysphagia, or complete dependence on others in the above activities being rated as 4). The scores for each individual function were summed to give the functional disability score. The global impression of disability was scored as follows: 0 for no myoclonus present; 1 for mild myoclonus, not annoying to patient; 2 for moderate myoclonus, annoying to patient; 3 for severe myoclonus causing distress to patient; and 4 for marked myoclonus causing the patient great distress.

Handwriting was assessed by asking the patient to sign their name, and copy a helix and spiral. This was scored on a scale of 0–5, with normal signature and copying being rated as 0, and the inability to hold a pen being rated as 5. The patient's assessment of his or her myoclonus, or, where this was not possible due to cognitive impairment, the assessment of a carer was recorded on a 10-cm visual analogue scale. A video recording of the clinical assessment of each patient was also made at the end of each course of treatment. This was independently scored by a second "blind" neurologist using the global disability scale.

Full blood count, erythrocyte sedimentation rate, electrolytes, random blood glucose levels, liver function tests, and anticonvulsant levels were monitored at the end of each course of treatment.

Statistical Methodology

An intention-to-treat analysis, which included all patients who entered the crossover group study, was carried out. Unless otherwise stated, the Wilcoxon 2 sample rank-sum test was used. This tests the treatment effect, the period effect, and the interaction between period and treatment (10). All tests were two-tailed and the level of significance was 5%. SAS 5.18 software was used for the analysis.

RESULTS

Of the 21 patients completing the trial, 10 had to be rescued prematurely during one of the two treatment phases due to an intolerable exacerbation of

their myoclonus. In all 10 cases, the relapse in their condition occurred during treatment with placebo, and not piracetam ($p < 0.01$). The frequency of relapse during the placebo phase did not differ significantly whether placebo formed the first (four patients relapsed) or second (six patients relapsed) course of treatment in the crossover trial. All 21 patients were assessed by the same "blind" neurologist at the end of each treatment phase, whether or not treatment courses were completed or prematurely terminated due to an intolerable exacerbation of myoclonus. The median scores on the stimulus sensitivity, motor impairment, writing, functional disability, global assessment, and visual analogue rating scales are shown for the end of the placebo and piracetam phases of the trial in Table 2. The median of the sum of these individual scores (total myoclonus) is also shown. Each of the individual and total test scores improved significantly during treatment with piracetam, with exception of the stimulus sensitivity score. Table 2 also shows the median percentage improvement for each of the test scores on treatment with piracetam, relative to placebo. The median improvement with piracetam ranged from 0 to 28.6% for the individual test scores. The total of the individual test scores improved by a median of 22.2%. There was no significant period effect or interaction between period and treatment. Videotape recordings of the assessments of each patient at the end of the two treatment phases were independently rated by a second "blind" neurologist using the global disability scale. There was a significant improvement in this score during treatment with piracetam ($p = 0.05$).

In individual patients, the total myoclonus score improved by as much as 98% during treatment with piracetam (Fig. 1). The two patients receiving piracetam monotherapy both showed improvements (36 and 42%) in their total score during treatment with active drug. Table 3 is a summary of the functional improvements made during piracetam treatment. Four patients only improved on the minority of individual test scores, and two failed to improve on any of the test scores. These six patients were considered nonresponders. Nonresponders were not systematically different from responders in their clinical characteristics or drug treatment.

Piracetam was well tolerated (Table 4). However, there were more epileptic fits during the placebo phase (eight fits) than during the piracetam phase (two fits) of the trial, despite the shorter duration of the placebo phase.

There was no significant change in the plasma level of sodium valproate during the two treatment phases. Too few patients were taking carbamazepine, phenytoin, or primidone to allow statistical evaluation of changes in these anticonvulsant levels. Plasma assay of clonazepam was not available. There was no change in full blood count, erythrocyte sedimentation rate, electrolytes, random blood glucose level, and liver tests during the trial.

DISCUSSION

Piracetam is shown to be an effective and useful symptomatic treatment for myoclonus of cortical origin, regardless of its underlying etiology. Other neurological abnormalities, such as ataxia, dystonia, and pyramidal deficits, were present in many of

TABLE 2. *Rating scores during treatment with placebo and piracetam*

Score	Placebo		Piracetam		p value[a]	Median improvement[b]
	Median	Range	Median	Range		
Stimulus sensitivity	0.0	0–14	0.0	0–13	0.079	0.0
Motor impairment	34.0	10–84	31.0	8–70	0.003	22.2
Writing	7.5	1–10	7.0	0–10	0.033	12.5
Disability	15.0	4–25	10.0	3–22	0.002	16.7
Global	2.0	1–4	2.0	1–3	0.014	28.6
Visual analogue	8.3	0–10	3.6	0–10	0.023	27.6
Total	66.3	23–147	52.4	18–119	0.002	22.2

The median and range of individual and total test scores are shown for the 21 patients with myoclonus. The median percentage improvement with piracetam treatment is also shown. Each patient was rated during treatment with placebo and piracetam. Only two of the patients were being treated with piracetam monotherapy on entry to the trial. The remaining 19 patients were receiving polytherapy and continued with their other antimyoclonic medication unchanged during the trial. Individual and total test scores, except stimulus sensitivity, improved significantly during treatment with piracetam.

[a] Wilcoxon two-sample rank-sum test, except for the global impression score in which the Cochran-Mantel-Haenszel test was used.

[b] Percentage improvement was calculated from (placebo score − piracetam score)/[(placebo score + piracetam score)/2] × 100 as described by Brouwers and Mohr (11).

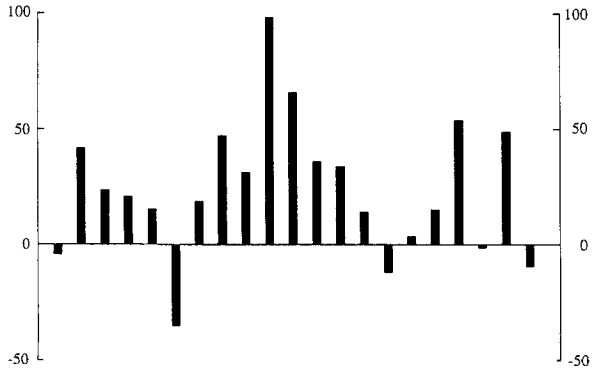

FIG. 1. The percentage change in total myoclonus score during treatment with piracetam in individual patients. Percentage change was calculated from (placebo total score − piracetam total score)/[(placebo total score + piracetam total score)/2] × 100, as described in ref. 11.

the patients studied and did not improve; these contributed to disability and limited the overall functional improvement produced by piracetam treatment. Piracetam was effective in combination with other antimyoclonic medication, but was also effective in monotherapy in two patients. It was well tolerated.

Although piracetam is effective in cortical myoclonus, Obeso et al. (8) found it to be ineffective in 16 patients with myoclonus of subcortical origin. This suggests that, where possible, electrophysiological assessment of the physiological type of myoclonus should be undertaken before considering treatment with piracetam. Even so, ~25% of patients with established cortical myoclonus fail to improve on treatment with piracetam (8).

The present study suggests that the abrupt discontinuation of piracetam may induce severe worsening of myoclonus and withdrawal seizures in some patients with cortical myoclonus. There were more seizures during treatment with placebo, despite the shorter duration of the placebo phase of the trial.

TABLE 3. *Improvement in function with piracetam treatment in the 21 patients during the placebo-controlled, double-blind trial*

Function	Worse[a]	Unchanged[a]	Improved[a]	Change from completely/partially dependent with placebo to independent but clumsy with piracetam
Walking	1	14	6	1
Dressing	0	11	10	4
Feeding	1	8	11	6
Washing	1	7	13	6

[a] Worse, unchanged, and improved mean that walking, dressing, feeding, or washing functional disability subscores (see Methods) during piracetam treatment were greater, equal to, or less than the respective subscores during placebo treatment.

TABLE 4. *Adverse events noted during the placebo-controlled, double-blind, crossover trial of piracetam*

	Placebo phase		Piracetam phase	
	Event	No. of patients	Event	No. of patients
General adverse events[a]				
	Upper respiratory tract infection	1	Sore throat and headache	1
	Asthma exacerbation	1		
	Urinary tract infection	1		
Epileptic seizures				
	Single fit	4	Single fit	2
	3 h of interrupted fits	1		
	Three fits during 3 days	1		

[a] One patient developed edema of the legs 2 days after starting open-label piracetam, and this persisted throughout the period of the double-blind trial.

The mechanism of action of piracetam in cortical myoclonus is obscure. Disturbances of serotonergic and GABAergic function are implicated in cortical myoclonus (1,2,12–14), but most studies have failed to show a significant effect of piracetam on the brain levels of these neurotransmitters (15,16). Piracetam is unlikely to act through the modulation of the effects of other antimyoclonic drugs, because it was effective in monotherapy, and did not alter the plasma level of sodium valproate.

In conclusion, piracetam is a useful treatment for cortical myoclonus, usually in combination with other antimyoclonic drugs. It is well tolerated, but may be associated with withdrawal seizures if discontinued abruptly. It is hoped that the present proof of the neuromodulatory effect of piracetam in myoclonus will stimulate further research into the mode of action of the nootropics.

Acknowledgment: We thank Dr. J. S. Duncan, Prof. A. E. Harding, Dr. S. D. Shorvon, Dr. J. A. Morgan-Hughes, and Dr. C. D. Ward for referring patients in this trial, Mrs. J. Taylor, and Dr. C. R. Wilsher for helpful discussion, and Miss C. Kurucz and Miss R. Adams for technical assistance. Financial support from U.C.B. Pharma is gratefully acknowledged. Dr. M. Salama and Dr. T. Waegemans are consultants to U.C.B. Pharma.

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