

# Piracetam relieves symptoms in progressive myoclonus epilepsy: a multicentre, randomised, double blind, crossover study comparing the efficacy and safety of three dosages of oral piracetam with placebo

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## Abstract

**Objective**—To compare the efficacy, tolerability, and safety of three daily dosage regimens of oral piracetam in patients with progressive myoclonus epilepsy.

**Methods**—Twenty patients (12 men, eight women), aged 17–43 years, with classical Unverricht-Lundborg disease were enrolled in a multicentre, randomised, double blind trial of crossover design in which the effects of daily doses of 9.6 g, 16.8 g, and 24 g piracetam, given in two divided doses, were compared with placebo. The crossover design was such that patients received placebo and two of the three dosage regimens of piracetam, each for two weeks, for a total treatment period of six weeks and thus without wash out between each treatment phase. The primary outcome measure was a sum score representing the adjusted total of the ratings of six components of a myoclonus rating scale in which stimulus sensitivity, motor impairment, functional disability, handwriting, and global assessments by investigators and patients were scored. Sequential clinical assessments were made by the same neurologist in the same environment at the same time of day.

**Results**—Treatment with 24 g/day piracetam produced significant and clinically relevant improvement in the primary outcome measure of mean sum score ( $p=0.005$ ) and in the means of its subtests of motor impairment ( $p=0.02$ ), functional disability ( $p=0.003$ ), and in global assessments by both investigator ( $p=0.002$ ) and patient ( $p=0.01$ ). Significant improvement in functional disability was also found with daily doses of 9.6 g and 16.8 g. The dose-effect relation was linear and significant. More patients showed clinically relevant improvement with the highest dosage and, in individual patients, increasing the dose improved response. Piracetam was well tolerated and adverse effects were few, mild, and transient.

**Conclusions**—This study provides further evidence that piracetam is an effective and safe medication in patients with Unverricht-Lundborg disease. In addition, it shows that a dose of 24 g is highly beneficial, more effective than lower doses

and that a dose-effect relation exists. There is considerable variation in optimal individual dosage.

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**Keywords:** double blind; myoclonus; piracetam; progressive myoclonus epilepsy

The progressive myoclonus epilepsies are characterised by severe myoclonus, grand mal seizures, and varying neurological deterioration.<sup>1–3</sup> The Baltic type of progressive myoclonus epilepsy, Unverricht-Lundborg disease, is one of the two classic types of the disorder, the other being Lafora body disease.<sup>4–7</sup> We now know that Unverricht-Lundborg disease is not confined to the Baltic area but occurs throughout the world, and that Unverricht-Lundborg disease, Mediterranean progressive myoclonus epilepsy, and some Ramsay-Hunt's syndromes are the same disease.<sup>8–12</sup>

The use of valproic acid and clonazepam has achieved remarkable progress in the treatment of progressive myoclonus epilepsy.<sup>13–15</sup> In addition, the avoidance of polytherapy and attention to other therapeutic modalities have contributed to patient wellbeing.<sup>16–18</sup> Myoclonic jerks, however, have remained incapacitating and drug resistant. Piracetam has considerable potential in the treatment of myoclonus both because it has been shown to be effective in the relief of myoclonic jerks and no interactions between piracetam and other anti-convulsant drugs have been reported.<sup>19–21</sup> Although higher doses seem to improve the response, a clear dose-response effect has not been shown and the optimal dose has not been established.

The aims of this study were, in a double blind setting, to confirm in a homogeneous group of patients with Unverricht-Lundborg disease, the efficacy, good tolerability, and safety shown in a previous double blind study in patients with progressive myoclonus epilepsy<sup>21</sup> and to attempt to determine the optimal dose and the presence of a dose-response relation. We therefore performed a multicentre, randomised, double blind, placebo controlled trial of crossover design<sup>22–24</sup> in which three daily dosage regimens were compared.

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**Table 1** Treatment sequences for two-week treatment periods with placebo and three dosage levels of piracetam in nine patients (this sequence was repeated once to allow inclusion of 18 patients)

1	2	3
X	A	B
X	B	C
X	C	A
A	X	C
B	X	A
C	X	B
A	C	X
B	A	X
C	B	X

X = placebo;

A = 9.6 g piracetam;

B = 16.8 g piracetam;

C = 24 g piracetam.

## Patients and methods

### PATIENTS

Twenty adults (12 men, eight women) whose mean age was 30 (range 17–43) years and mean weight 82 (range 50–117) kg from four centres in Finland were enrolled in the study. All patients had classic Unverricht-Lundborg disease with onset between the ages of 6 and 15 years; stimulus sensitive myoclonus, generalised seizures, and abnormal EEG recordings with photosensitivity and spike and wave paroxysms.<sup>4–7</sup> The diagnosis was confirmed by genetic analysis showing decreased cellular mRNA encoded by the gene cystatin B.<sup>9</sup> The mean duration of Unverricht-Lundborg disease was 21 (range 10–31) years. All patients were on medication and dosage had been stable for at least one month before the trial. Patients with mild Unverricht-Lundborg disease (sum score <3) were not included. Pregnant or lactating females and women of childbearing age not using adequate contraception were not included in the study. Other reasons for exclusion were clinically relevant abnormalities in laboratory tests, participation in a drug trial during the three months before enrolment, and participation of a third member of the family in the study. Informed consent according to the Helsinki II declaration was obtained from all patients. The study was approved by local ethics committees and conducted according to Finnish guidelines for good clinical practice.

### STUDY DESIGN AND TREATMENTS

Study treatments were three daily dosages of piracetam—9.6 g, 16.8 g, or 24 g and placebo. Doses between 7.2 g and 16.8 g/day piracetam had previously been shown to be effective.<sup>21</sup> All piracetam and placebo tablets were identical in appearance, taste, and smell and blindness was maintained by a dosage of 10 tablets twice daily to all patients during placebo and active treatment phases. The crossover study design

chosen was a control balanced residual effect design appropriate for the comparison of several treatments with a control group.<sup>24</sup> Eighteen patients were randomly allocated to treatment. Patients received one of the nine sequences of treatments (table 1) so that each received placebo and two of the three dosage regimens of piracetam. This sequence was repeated once. Each treatment period lasted two weeks; there was no wash out period between treatments because it had been shown in a previous study that no carry over effect occurred.<sup>21</sup> The study thus lasted for six weeks in each patient. The balanced design required 18 patients in whom data were evaluable; any patient who discontinued the study or whose data were not valid for analysis was therefore replaced. Two of 20 patients enrolled were replaced because their symptoms on entry were too mild (sum score on entry <3).

### ASSESSMENTS

Clinical assessment was performed on entry to the study and after each two week treatment period by the same neurologist in the same environment at the same time of day. Six indices were assessed: stimulus sensitivity, motor impairment, functional disability, handwriting, and global assessments by investigators and patients. These indices constituted a myoclonus rating scale described by Truong and Fahn<sup>25</sup> and adapted by Brown *et al.*<sup>21</sup> Briefly, each of the six components or subtests was scored, the scores for each were added, and the total scores of the six subtests adjusted so that the sum score for each patient was rated from 0 (best) to 10 (worst). Patients were scored at baseline and at the end of each two week treatment period. The mean sum score was the primary measure of outcome and, based on the results of a previous double blind study, a difference of 1 unit was regarded as clinically relevant.<sup>21</sup>

Stimulus sensitivity and motor impairment were evaluated and scored in eight body areas: eyes, face, neck, trunk, right and left arm, right and left leg and, for motor impairment, type, frequency, and severity were assessed. In the assessment of functional disability speech, swallowing, eating, washing, dressing, walking, and handwriting were rated. Handwriting was also scored as a separate subtest. Global assessment by investigators and patient self assessment using a visual analogue scale were also rated. Table 2 shows the components of each subtest and the method of scoring.

Compliance with treatment was evaluated by counting unused tablets when test bottles were returned at the end of each treatment period. All complaints and other adverse events were recorded at each visit. Haemoglobin, white cell and platelet counts, and liver function were tested before and after each treatment period. Serum sodium, potassium, and creatinine were measured at the beginning and end of the trial.

### STATISTICS

#### Sample size

The analysis of variance for the effect of treatment in the previous crossover trial yielded a

**Table 2** Summary of the variables scored and the method of scoring in the six subtests of the myoclonus rating scale<sup>21–25</sup>

	Score
(A) Stimulus sensitivity: Stimuli: tendon tap to finger or toe, pinprick, loud noise, flash of bright light, visual threat Range 0–8 for each of these 5 stimuli	0–40
(B) Motor impairment: Spontaneous myoclonus: 0–32 (score 0–4 for each of 8 areas) Action myoclonus frequency: 0–32 (score 0–4 for stereotyped movement in each of 8 areas) Action myoclonus severity: 0–32 (score 0–4 according to degree of interference with function)	0–96
(C) Functional disability: Score 0–4 for degree of impairment of speech, swallowing, eating (knife and fork), washing, dressing, walking, handwriting	0–28
(D) Handwriting: Signing name 0–5; copying 0–5	0–10
(E) Global assessment by investigator: Score 0–4 for from none to severe	0–4
(F) Global assessment by patient: Score 0–10 using 10 cm visual analogue scale	0–10
Adjusted sum score (A/40 + B/96 + C/28 + D/10 + E/4 + F/10) × 10/6)	0–10

Type, frequency, and severity of myoclonus evaluated with scoring for stimulus sensitivity and motor impairment were assessed in eight body areas: eyes, face, neck, trunk, right and left arm, right and left leg.

Table 3 Scores for the primary outcome measure, the adjusted sum score of the myoclonus rating scale and its subtests after two weeks of treatment with placebo and daily doses of 9.6 g, 16.8 g, and 24 g piracetam

Subtest	Placebo (n = 18)	Piracetam			p Value*
		9.6 g (n = 12)	16.8 g (n = 12)	24 g (n = 12)	
Adjusted sum score	5.2 (4.3–6.2)	4.9 (3.9–5.9)	4.6 (3.6–5.6)	4.1 (3.1–5.1)	0.005
Stimulus sensitivity	13.2 (7.2–19.1)	13.0 (6.6–19.3)	11.1 (4.8–17.4)	9.5 (3.2–15.8)	0.07
Motor impairment	57.0 (49.8–64.3)	59.0 (50.6–67.5)	52.2 (43.7–60.7)	47.0 (38.5–55.5)	0.02
Functional disability	13.3 (9.9–16.8)	11.5 (7.9–15.1)	11.5 (7.9–15.0)	10.5 (7.0–14.1)	0.003
Handwriting	5.2 (3.8–6.5)	5.3 (3.5–6.5)	5.0 (3.5–6.5)	4.7 (3.2–6.2)	0.43
Investigator's global assessment	2.8 (2.3–3.4)	2.5 (1.9–3.1)	2.5 (1.9–3.1)	2.2 (1.6–2.8)	0.002
Patient's global assessment by VAS	50.8 (41.2–60.4)	45.2 (33.7–56.7)	40.3 (28.8–51.8)	34.4 (22.9–45.9)	0.01

Values are least square means and 95% CIs.

\*p Values of paired comparisons of piracetam (24 g/day) and placebo resulting from analysis of variance (ANOVA).

mean square error of 0.55.<sup>21</sup> The effect of treatment in that trial was a reduction in the mean adjusted sum score from 5.0 to 3.8 (a difference of 1.2). In the present trial, the aim was to show, with a probability of 90% and a significance level of 0.05, a difference of 1 unit in the mean adjusted sum score between the placebo group and a group receiving piracetam. It was estimated that 12 patients were required. Because of the control residual balanced design, each patient received placebo and two of the three dosages of piracetam; 18 patients were required to show such a difference between placebo and each dosage level of piracetam.

Quantitative variables were described by means, SD, and ranges and qualitative variables by frequencies and percentages. Inferential analysis was performed for all end points of the clinical assessment scale. To test for effects of treatment, period, and first order carry over, analysis of variance (ANOVA) using the SAS proc mixed procedure was performed.<sup>23</sup> The least square means and 95% confidence intervals (95% CIs) for each treatment group were calculated from this analysis. The assumption

of normality was checked by means of normal probability plots of residuals. Regression analysis was performed to test the linearity of the dose-effect relation of the mean sum score, adjusted for patient and period. Efficacy was analysed in all patients with valid data and, to be sure that inclusion of two replacement patients had not influenced the results, an intention to treat analysis was also performed.<sup>24</sup> There were no missing data. All computations and analyses were performed blind, using SAS software and carried out by ID<sup>28</sup>, Brussels, Belgium.

## Results

Eighteen eligible patients completed the study according to the protocol. Tablet counts showed that compliance with treatment was complete.

Table 3 summarises the results of clinical assessment after placebo and each dosage level of piracetam using the myoclonus rating scale. These are presented for the adjusted sum score, the primary outcome variable, and each of its six subtests. We found significant improvement (p=0.005) in the mean sum score with a daily dose of 24 g piracetam (table 3). Improvement at this dose level occurred in mean scores for all six subtests and reached significance for motor impairment (p=0.02), functional disability (p=0.003), and global assessments by investigators (p=0.002) and patients (p=0.01) (table 3). Stimulus sensitivity decreased but not significantly. Improvement in handwriting in five of 10 patients did not produce a significant decrease in mean score. Scores for functional disability also showed significant improvement (p=0.04) at the lower dosage levels of 9.6 g and 16.8 g but improvements in other subtests did not attain significance at these doses.

Table 4 shows the significant improvement in functional disability on each dosage level of piracetam in terms of the differences between piracetam and placebo groups in changes from baseline. Speech improved in five of 13 patients in whom it had been abnormal to the point where it was easily understandable. Feeding improved in seven of 16 patients with feeding problems and five patients treated with piracetam were able to eat normally or alone with a fork or spoon. In four of 10 patients with difficulty in swallowing, problems disappeared after treatment. For dressing, three of 11 dependent patients became independent.

Table 4 Functional disability: improvement from baseline assessed by difference between improvement with placebo and improvement with piracetam at each dose expressed as percentages with 95% CIs

Dosage	Percentage difference between placebo and piracetam (95% CI)	
Dressing		
9.6	8	(-0.20 to 0.36)
16.8	8	(-0.08 to 0.24)
53.0	25	(0.01 to 0.50)
Feeding		
9.6	33	(0.06 to 0.60)
16.8	33	(0.06 to 0.60)
24.0	33	(0.06 to 0.60)
Speech		
9.6	25	(-0.16 to 0.66)
16.8	17	(-0.04 to 0.38)
24.0	25	(0.01 to 0.50)
Swallowing		
9.6	17	(-0.04 to 0.38)
16.8	8	(-0.20 to 0.36)
24.0	25	(-0.09 to 0.59)
Toilet		
9.6	25	(0.01 to 0.50)
16.8	25	(0.01 to 0.50)
24.0	25	(-0.11 to 0.51)
Walking		
9.6	8	(-0.08 to 0.24)
16.8	17	(-0.14 to 0.48)
24.0	33	(0.06 to 0.60)

Seven of 17 improved in managing the toilet and three patients no longer experienced difficulty. Three of 10 dependent patients became independent. Of 12 patients confined to a wheelchair, none was able to walk after two weeks of treatment but abnormal walking improved in four of six patients. Illegible or near illegible handwriting became legible in five of 10 patients. The lowest doses at which these improvements occurred varied but, when an effect was seen at the lowest dose, it was also present—and usually more pronounced—at the highest dose. Table 4 shows that the 95% CIs rarely reached zero.

Regression analysis on the sum score showed a linear and highly significant dose-effect relation ( $p=0.003$ ). An increase of 1 g in the daily dose of piracetam led to a decrease in the mean sum score of 0.04 points. Although more patients showed clinically relevant improvement at doses of 16.8 g and 24 g/day than at 9.6 g, there was substantial individual variation and the effect of a given dose differed in different patients. There was no evidence of period or carry over effects.

After the double blind study, 17 of 20 patients wished to continue with piracetam without knowing the results of the trial. Two of these patients in whom no clear effect was apparent on the myoclonus assessment scale felt better subjectively and still continued with piracetam six months after the trial. We also thought that several relevant improvements, especially better initiative and more energy, were not able to be measured with the clinical assessment scale.

Adverse events were reported on 29 occasions, including 12 during the placebo period, and consisted of convulsions (seven), fatigue (five), worsening of myoclonus (four), gastrointestinal symptoms (three), headache (two), vertigo (two), depression (one), waking up at night (one), leg oedema (one), hypernatraemia (two), and hyperkalaemia (one). Eight epileptic seizures were reported in three patients, of which six occurred during the placebo period or after termination of the trial, and two occurred during dosage with 9.6 g/day piracetam, after a decrease from a higher dosage. In two of these patients, convulsions were rare before the trial; the third patient had experienced seizures at regular intervals, but they occurred more often during the trial. Two further patients who usually had one to three convulsions each week remained symptom free during the study.

Minor and clinically unimportant abnormalities were found at baseline in haemoglobin, white cell counts, and liver function. These were uninfluenced by treatment and no other laboratory test abnormalities occurred during the trial.

## Discussion

This double blind study has shown clear improvement in myoclonus in patients with Unverricht-Lundborg disease at a dose of 24 g/day. We found significant and clinically relevant improvement in the mean sum score of the myoclonus rating scale, the primary

outcome index, and in the subtests of motor impairment, functional disability, and global assessment by both investigator and patient. The dose-response relation was linear between daily doses of 9.6 g, 16.8 g, and 24 g piracetam and significant improvement in functional disability also occurred at both lower dosage levels.

Our results are in accord with the improvement in myoclonus shown in the one previous double blind study with piracetam by Brown *et al.*<sup>21</sup> which confirmed the response reported in previous open trials. In that study, the dose was increased in an open run in phase until an optimal response was achieved; daily doses ranged between 7.2 g and 16.8 g daily with a median dose of 16.8 g piracetam. Response was then confirmed in the double blind phase of the trial. The study design did not permit assessment of a dose-response relation or optimal dosage.

Although improvement occurred in the present study at a dose of 16.8 g/day, this was less than that shown by Brown *et al.*<sup>21</sup> This may have been due to differences in study design and patient selection. For example, mean patient weight was 81.9 kg in the present trial compared with 68 kg<sup>21</sup> and concentrations of piracetam in plasma and CSF will be less in obese subjects.

Although some patients showed no clear improvement when assessed by the myoclonus rating scale, they felt better subjectively and wanted to continue treatment. Piracetam has been reported to possess a beneficial effect in patients with mild dementia and with impaired cognitive function.<sup>26 27</sup> It may also increase vigilance<sup>28</sup> and improve dyslexia.<sup>29 30</sup> These effects may partly explain our findings.

Adverse events were uncommon and occurred mostly during the low dose piracetam or placebo periods; few occurred at the highest dose level. Some patients experienced tiredness during several treatment periods, and transient insomnia and depression were reported in one patient each on a daily 24 g dose of piracetam. Gastrointestinal complaints were few. Piracetam was well tolerated and no laboratory indices showed drug related alterations.

Six of eight seizures were withdrawal seizures, and those in two other patients occurred after a sudden decrease in dose. Sudden discontinuation of piracetam has previously been reported to cause withdrawal seizures.<sup>21</sup>

The pathophysiology of myoclonus awaits clarification. Neither do we know how piracetam exerts its effect. The identification of a gene, encoding for cystatin B, which is responsible for the primary defect in Unverricht-Lundborg disease, provides a molecular target for understanding the pathophysiology and therapy of myoclonus.<sup>9</sup> Piracetam has been shown to alter the physical properties of the cell membrane and to increase its fluidity and also to protect the cell against hypoxia.<sup>31 32</sup> It increases red cell deformability and normalises aggregation of hyperactive platelets.<sup>33</sup> Piracetam has no effect on indices of cardiovascular, respiratory, gastrointestinal, or renal function.



The progression of Unverricht-Lundborg disease is nowadays much slower and life expectancy seems much better than 20 years ago,<sup>7 17</sup> when patients were often confined to bed and died of infections or other incidental causes. In the 1960s and early 1970s the mean survival period was about 14 years after the appearance of the first symptoms.<sup>4 7</sup> Today, most patients live for 30 years or more after the onset of progressive myoclonus epilepsy. Improvement in general condition and life expectancy is due to the increase in social contacts, intensive rehabilitation,<sup>8</sup> treatment of infections, and avoidance of phenytoin and barbiturates<sup>8</sup> in medication. If myoclonic jerks can be relieved, the outlook for rehabilitation and the prognosis of progressive myoclonus epilepsy will improve further.

### Conclusion

The improvement shown in this double blind trial is further evidence of the beneficial effect of piracetam in myoclonus previously described in case reports, open trials,<sup>20 34</sup> and one double blind study.<sup>21</sup> In the present study, 24 g/day piracetam was beneficial. A linear dose-effect relation was evident. The optimal individual dose of piracetam seems to range between 7.2 and 24 g/day. Sudden withdrawal of the drug should be avoided as this may cause withdrawal seizures. Every patient with myoclonic symptoms warrants a trial of therapy with piracetam.

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