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Pyridostigmine in postpolio syndrome: no decline in fatigue and limited functional improvement


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Objectives: To investigate the effect of pyridostigmine on fatigue, physical performance, and muscle function in subjects with postpoliomyelitis syndrome.

Methods: 67 subjects with increased fatigue and new weakness in one quadriceps muscle showing neuromuscular transmission defects, were included in a randomised, double blind, placebo controlled trial of 60 mg pyridostigmine four times a day for 14 weeks. Primary outcome was fatigue (on the ‘energy’ category of the Nottingham health profile). Secondary outcomes included two minute walking distance and quadriceps strength and jitter. Motor unit size of the quadriceps was studied as a potential effect modifier. The primary data analysis compared the changes from baseline in the outcomes in the last week of treatment between groups.

Results: 31 subjects treated with pyridostigmine and 31 subjects treated with placebo completed the trial. No significant effect of pyridostigmine was found on fatigue. The walking distance improved more in the pyridostigmine group than in the placebo group (by 7.2 m (6.0%); p<0.01). Subgroup analysis showed that a significant improvement in walking performance was only found in subjects with normal sized motor units. Quadriceps strength improved more in the pyridostigmine group than in the placebo group (by 6.7 Nm (7.2%); p=0.15). No effect of pyridostigmine was found on jitter.

Conclusions: Pyridostigmine in the prescribed dose did not reduce fatigue in subjects with postpoliomyelitis syndrome. However, it may have a limited beneficial effect on physical performance, especially in subjects with neuromuscular transmission defects in normal sized motor units.

Subjects with postpoliomyelitis syndrome often complain of fatigue and a deterioration in functional abilities. These symptoms may, in part, reflect neuromuscular transmission defects.

The hypothesis in postpoliomyelitis syndrome is that the enlarged motor units which were formed during the recovery phase lose their ability to maintain all their sprouts, which slowly deteriorate. This deterioration may be accompanied by increasing neuromuscular transmission defects as a result of progressive dysfunction of acetylcholine synthesis and release. The severity of these transmission defects might increase with increasing motor unit size. Furthermore, polio patients, especially those with postpoliomyelitis syndrome, are often unable to activate their muscles fully, which may be related to neuromuscular transmission defects.

Pyridostigmine, an anticholinesterase inhibitor, prolongs the effectiveness of acetylcholine. In open studies of pyridostigmine in patients with postpoliomyelitis syndrome, both neuromuscular transmission defects and perceived fatigue decreased. However, a randomised double blind trial failed to confirm a beneficial effect. In that study, patients were not selected on the basis of a predefined level of fatigue or on the presence of neuromuscular transmission defects, and the responsiveness of the primary outcome measure, the short form 36 item questionnaire (SF-36), may have been insufficient to detect change. Furthermore, the investigators questioned the adequacy of 180 mg of pyridostigmine a day.

The present placebo controlled double blind trial was undertaken to study the effect of 240 mg pyridostigmine a day in a selected group of subjects with postpoliomyelitis syndrome who had an increased level of fatigue and proven neuromuscular transmission defects in a symptomatic quadriceps muscle—a muscle that is functionally important for locomotion. Our primary aim was to investigate the effect of pyridostigmine on perceived fatigue. Secondary objectives were to investigate the effects on physical performance and muscle function.

METHODS

Patient selection and baseline assessment

Ambulatory subjects with postpoliomyelitis syndrome were included if they had the following:

- a fatigue score of 10 points or more on the short fatigue questionnaire;
- symptoms of postpoliomyelitis muscle dysfunction in at least one quadriceps muscle;
- neuromuscular transmission defects (mean jitter >30 µs or more than two jitter values of >40 µs) in the symptomatic quadriceps muscle on single fibre electromyographic stimulation (S-SFEMG);
- a minimum quadriceps strength of 30 Nm;
- age between 18 and 70 years.

Exclusion criteria were significant neurological, orthopaedic, cardiovascular, pulmonary, or endocrine disorders, and anaemia or thyroid dysfunction, both checked by blood tests. The quadriceps with the severest symptoms was investigated.

The duration of symptoms of postpoliomyelitis syndrome, the severity of paresis of the legs, and motor unit size of the
lateral vastus were recorded at baseline. The severity of paresis was calculated as a sum score of 16 lower extremity muscle groups, based on manual muscle testing. The size of at least 10 motor units was estimated from multichannel surface EMG recordings. Enlarged mean motor unit size was defined as $> 4 \text{mVms}$. The medical ethics committees of the hospitals involved approved the study. All subjects gave their written informed consent.

**Randomisation, blinding, and treatment regimen**

Randomisation of treatment allocation was done in blocks of four. All treatment allocations were concealed for the patients as well as the researchers. The data analyst remained blinded until after the primary outcome analyses.

A dose of $60 \text{mg}$ pyridostigmine four times a day was given for 14 weeks. The dose was gradually increased during the first six days from $4 \times 10 \text{mg}$ to $4 \times 60 \text{mg}$, to reduce the chance of adverse effects. From the fourth day onwards, $0.125 \text{mg}$ atropine was added at each dose to mask the parasympathetic effects of pyridostigmine. The placebo treated subjects also received pyridostigmine during the first three days in the same incremental dose to improve blinding. Subsequently, the pyridostigmine was phased out in two days, and from day 6 onwards placebo pyridostigmine was given. From day 4 onwards this was combined with placebo atropine. Drug treatment was taken 1.5 to 2 hours before each study visit. Compliance was checked by counting the remaining pills.

**Study design**

Subjects were measured five times: two baseline visits, with a three week interval to check for learning effects, a visit in the fifth week of treatment and three weeks after cessation of treatment. For each subject, all visits were scheduled at the same time of day. The drug treatment started two weeks after the second baseline visit (range one to three).

**Outcome measures**

Primary outcome was the category “energy” in the Nottingham health profile (NHPE). Unweighted sum scores were formed by the median baseline value. All differences were compared by the Mann-Whitney-U test. The sample size was set at 64. The primary analysis compared the subjects receiving pyridostigmine and the subjects receiving placebo with regard to changes in the outcome measures of treatment between groups. The minimum clinical relevant improvement in the secondary outcome measures was set at 10%. The analyses were based on an intention to treat approach. Subgroup analyses were done for muscle fatigability of the lateral vastus, determined with surface EMG during a 30 s sustained isometric contraction of the MVC that was obtained at the first baseline visit. Muscle fatigue was quantified as the difference in the median frequency (MF) between the first five and the last five seconds ($MF_{0.0} - MF_{25.0}$).

Muscle fatigue of the lateral vastus, determined with surface EMG during a 30 s sustained isometric contraction of the MVC was calculated from the increment in force produced by stimulation during the MVC ($a$) and the force due to control stimulation ($b$) as $(1 - a/b) \times 100$. The highest MVA of three attempts was used for the analysis.

**Questionnaires**

The following questionnaires were used:

- The fatigue severity scale (FSS), with a score ranging from 1 (no effect of fatigue on daily life) to 7 (severe, disabling fatigue). The subjective benefit of the treatment, with two questions: (1) “What, in your opinion, is the effect of the treatment?”, with answers ranging from 1: “very much worse”; to 7: “very much improved”; and (2) “Compared to the period before treatment, your fatigue complaints have ...?”, with answers ranging from 1: “greatly increased”, to 7: “greatly decreased”. A score of 4 indicated no change.

**Physical performance**

Physical performance was assessed in the following ways:

- The distance walked in two minutes at comfortable speed, and maximum walking performance—the time needed to walk 75 m as fast as possible.
RESULTS
Sixty seven of the 101 subjects who were screened were included (fig 1). The two groups were comparable with respect to demographic and baseline characteristics (table 1).

Two subjects were excluded after treatment allocation because of thyroid dysfunction and anaemia. Two subjects withdrew from the study, one (pyridostigmine) after four weeks of treatment because of personal circumstances, and one (placebo) after six weeks of treatment because of dissatisfaction with the procedures. In general, the treatment was well tolerated. One subject (pyridostigmine) discontinued the drug because of severe diarrhoea, and was lost to follow up for personal reasons.

Compliance and blinding
Compliance was good. Fifty five of the 62 subjects who completed the study took at least 90% of their drug dose. Only two subjects (placebo) took less than 80% of their dose. The blinding code was not broken during the trial, and the blinding was successful—68% of the subjects receiving pyridostigmine and 47% of the subjects receiving placebo guessed their actual treatment correctly (p = 0.37). The investigator guessed correctly for 39% of the pyridostigmine treated subjects and for 42% of the placebo treated subjects (p = 0.20).

Outcome
There was no significant difference in change on the primary outcome NHP_e between the two groups during the treatment period (table 2). In the 14th week of treatment, a significant reduction of 36% was found in both groups. No difference in change on the FSS or in the subjective benefit of the treatment was found between the two groups; both improved significantly during the treatment period. In the 14th week of treatment, the walking distance improved more in the pyridostigmine group than in the placebo group (by 7.2 m (6.0%); p = 0.003). No effect of pyridostigmine was found on maximum walking performance. Three weeks after the treatment period the pyridostigmine group improved significantly more than the placebo group on walking distance and maximum walking performance. No difference in change in the duration of walking was found between the two groups. Walking duration increased significantly in the pyridostigmine group.

There was no difference in change in quadriceps strength between the two groups. In the 14th week of treatment, significant improvements were found in both groups. In the
last week of treatment, 58% of the subjects in the pyridostigmine group improved on both quadriceps strength and walking distance, whereas 13% of the subjects in this group did not improve on either of these outcome measures (p<0.05, χ² test). In the placebo group, 32% improved on both outcome measures, whereas 19% did not (p = 1.00).

In 24 subjects (10 pyridostigmine, 14 placebo), MVA could not be measured owing to inability to stimulate the quadriceps to exert at least 25% of the MVC (n = 21) or because of intolerance of the measurement (n = 3). In the fifth week of treatment and three weeks after the treatment period, the quadriceps had improved significantly more in the pyridostigmine group than in the placebo group.

Data on muscle fatigability were missing for seven subjects in both the pyridostigmine and the placebo groups owing to recording artefacts. Muscle fatigability did not change in either group.

Jitter values were missing for three subjects in the placebo group (intolerance in two, technical failure in one) in the last week of treatment. No difference in change in jitter was found between the two groups.

**Subgroup analyses**

Motor unit size was missing in four subjects (three pyridostigmine, one placebo) owing to technical failures.

Motor unit size was increased in 23 subjects (12 pyridostigmine, 11 placebo) and was normal in 35 subjects (16 pyridostigmine, 19 placebo). For the subjects with enlarged motor units, no difference in change between the two groups was found for any outcome measure. For the subjects with normal sized motor units, walking distance improved 9.5 m more (8.4%; p = 0.002), and maximum walking performance 2.9 s more (4.5%; p = 0.03) in the pyridostigmine group than in the placebo group.

No differences in effects were found for subgroups based on walking distance or quadriceps strength.

**DISCUSSION**

Our study provided no evidence of any benefit of pyridostigmine in reducing fatigue in patients with postpoliomyelitis syndrome with increased fatigue and neuromuscular transmission defects in a quadriceps muscle with new neuromuscular symptoms. The only significant difference in change between the two study groups in the 14th week of treatment was for walking distance, though the improvement of 6% was less than considered clinically relevant. The main question to be answered is whether pyridostigmine is indeed ineffective as a treatment for postpoliomyelitis syndrome, or whether the negative result reflects shortcomings of the study.

**Was the dose of pyridostigmine adequate?**

Taking into account the negative result of a randomised controlled trial with 180 mg a day,12 we increased the dose of pyridostigmine to 240 mg. To assess whether this dose was pharmacologically effective, changes in neuromuscular transmission defects were monitored (S-SFEMG). The fact that no significant improvement in neuromuscular transmission was found in the pyridostigmine group might suggest that the dose of 240 mg was not adequate. However, the large standard deviation of the difference in jitter found in the placebo group (table 2), probably caused by large variation in neuromuscular transmission defects between endplates, indicates that the reproducibility of jitter was poor. Thus jitter was not an appropriate measure to establish the effectiveness of the pyridostigmine dose.

Nonetheless, plasma concentrations of pyridostigmine can vary greatly between individuals,13 and the dose may have been insufficient for an unknown number of subjects. This implies that individual adjustment may be required to obtain an effective dose.

**Was the ability to detect an effect of pyridostigmine adequate?**

The sample size of the study population was calculated with an expected standard deviation of 30 in the change in NHP₂E score.14 The NHP₂E scores which were obtained were in agreement with this assumption and confirmed an adequate power calculation. However, the NHP₂E showed a substantial ceiling effect at baseline, where 15 subjects (23%) had a score of 0. In addition, the NHP₂E scores in the placebo group decreased significantly during the treatment period. To demonstrate a beneficial effect of pyridostigmine, the scores in the pyridostigmine group would have to decrease by more than 33%, which was only found possible in 15 subjects.

Fatigue was also measured with the FSS, which has more response choices and showed no ceiling effect. As the FSS also failed to improve with pyridostigmine, the lack of effect on the NHP₂E cannot be attributed to an insufficient ability to detect change.

**Does pyridostigmine have an effect on muscle function?**

In this study, many comparisons were made and statistically tested. By chance, multiple testing can yield significant differences that do not reflect true differences and may produce misleading results. Some of the significant differences found—for instance, on maximum walking performance and MVA three weeks after treatment—may therefore be coincidental. However, if these differences had resulted from chance alone, they would have been equally distributed over the two treatment groups. The significant improvements in walking distance, the duration of walking, quadriceps strength, and MVA were all in favour of the pyridostigmine...
Table 2 Changes in outcome measures from the second baseline measurements at five and 14 weeks of treatment and three weeks after end of treatment, according to treatment group

<table>
<thead>
<tr>
<th></th>
<th>Week 5 of treatment</th>
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<th>Week 14 of treatment</th>
<th></th>
<th>Three weeks after end of treatment</th>
<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td>PSM (n = 31)</td>
<td>Placebo (n = 31)</td>
<td>∆ (95% CI) p value</td>
<td>PSM (n = 31)</td>
<td>Placebo (n = 31)</td>
<td>∆ (95% CI) p value</td>
</tr>
<tr>
<td>NHPE (range 0–100)</td>
<td>-10.8 (35.9)</td>
<td>-10.8 (26.4)</td>
<td>0.0 (16.0 to -16.0) 1.00</td>
<td>-18.3 (36.4)</td>
<td>-17.2 (33.2)</td>
<td>-1.1 (-18.8 to 16.6) 0.90</td>
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<tr>
<td></td>
<td>p = 0.11</td>
<td>p = 0.03</td>
<td></td>
<td>p = 0.01</td>
<td>p = 0.01</td>
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<tr>
<td>FSS (range 1–7)</td>
<td>-0.2 (0.7)</td>
<td>-0.4 (0.5)</td>
<td>0.1 (-0.2 to 0.4) 0.44</td>
<td>-0.6 (0.9)</td>
<td>-0.4 (0.9)</td>
<td>-0.2 (-0.6 to 0.3) 0.48</td>
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<tr>
<td></td>
<td>p = 0.07</td>
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<td>p &lt; 0.01</td>
<td>p &lt; 0.01</td>
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<tr>
<td>Subjective benefit of treatment</td>
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<tr>
<td>Question 1</td>
<td>0.5 (0.7)</td>
<td>0.5 (0.8)</td>
<td>-0.1 (-0.5 to 0.3) 0.61</td>
<td>0.5 (0.9)</td>
<td>0.5 (0.9)</td>
<td>-0.1 (-0.5 to 0.4) 0.78</td>
</tr>
<tr>
<td></td>
<td>p &lt; 0.01</td>
<td>p &lt; 0.01</td>
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<td>p &lt; 0.01</td>
<td>p &lt; 0.01</td>
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<tr>
<td>Question 2</td>
<td>0.4 (0.8)</td>
<td>0.4 (0.9)</td>
<td>-0.1 (-0.5 to 0.4) 0.76</td>
<td>0.5 (0.9)</td>
<td>0.5 (0.9)</td>
<td>-0.1 (-0.5 to 0.4) 0.78</td>
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<td></td>
<td>p &lt; 0.01</td>
<td>p &lt; 0.01</td>
<td></td>
<td>p &lt; 0.01</td>
<td>p &lt; 0.01</td>
<td></td>
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<tr>
<td>Two minute walking distance (m)</td>
<td>8.6 (9.9)††</td>
<td>5.8 (5.9)</td>
<td>2.8 (-1.4 to 7.0) 0.18</td>
<td>10.2 (9.4)</td>
<td>3.0 (8.8)</td>
<td>7.2 (2.6 to 11.9) 0.03</td>
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<tr>
<td></td>
<td>p &lt; 0.001</td>
<td>p &lt; 0.001</td>
<td></td>
<td>p &lt; 0.001</td>
<td>p &lt; 0.07</td>
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</tr>
<tr>
<td>Max walking performance, 75 m (s)</td>
<td>-1.1 (3.5)††</td>
<td>0.5 (5.8)</td>
<td>-1.5 (-4.0 to 0.9) 0.21</td>
<td>-1.6 (4.4)</td>
<td>0.1 (4.0)††</td>
<td>-1.7 (-3.9 to 0.5) 0.13</td>
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<tr>
<td></td>
<td>p = 0.09</td>
<td>p = 0.76</td>
<td></td>
<td>p = 0.06</td>
<td>p = 0.89</td>
<td></td>
</tr>
<tr>
<td>Duration of walking (% of total time)</td>
<td>1.5 (1.3)††</td>
<td>1.0 (1.7)</td>
<td>0.5 (-0.8 to 1.9) 0.42</td>
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<tr>
<td></td>
<td>p &lt; 0.01</td>
<td>p = 0.02</td>
<td></td>
<td>p &lt; 0.01</td>
<td>p = 0.02</td>
<td></td>
</tr>
<tr>
<td>Quadriceps strength (Nm)</td>
<td>6.7 (1.7)†</td>
<td>5.0 (1.9)</td>
<td>1.7 (-5.3 to 8.7) 0.63</td>
<td>12.7 (2.4)</td>
<td>6.0 (1.3)</td>
<td>6.7 (-2.4 to 15.7) 0.15</td>
</tr>
<tr>
<td></td>
<td>p = 0.01</td>
<td>p = 0.06</td>
<td></td>
<td>p &lt; 0.01</td>
<td>p &lt; 0.02</td>
<td></td>
</tr>
<tr>
<td>Max voluntary activation (range 0–100)</td>
<td>6.5 (143)††</td>
<td>-4.7 (11.3)††</td>
<td>11.1 (3.0 to 19.3) 0.01</td>
<td>7.7 (14.2)††</td>
<td>1.1 (14.2)††</td>
<td>6.6 (-2.2 to 15.5) 0.14</td>
</tr>
<tr>
<td></td>
<td>p = 0.04</td>
<td>p = 0.09</td>
<td></td>
<td>p = 0.02</td>
<td>p = 0.74</td>
<td></td>
</tr>
<tr>
<td>Muscle fatiguability (MF0.1–MF25–30)</td>
<td>0.1 (2.9)</td>
<td>-0.0 (3.5)††</td>
<td>0.2 (-1.6 to 1.9) 0.85</td>
<td>0.9 (3.4)†</td>
<td>0.2 (3.3)†</td>
<td>0.7 (-1.1 to 2.6) 0.43</td>
</tr>
<tr>
<td></td>
<td>p = 0.82</td>
<td>p &lt; 0.01</td>
<td></td>
<td>p &lt; 0.01</td>
<td>p &lt; 0.01</td>
<td></td>
</tr>
<tr>
<td>NMT, jitter (μs)</td>
<td>-5.6 (16.0)</td>
<td>-2.8 (21.1)††</td>
<td>-2.8 (-12.5 to 6.9) 0.57</td>
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<tr>
<td></td>
<td>p = 0.06</td>
<td>p = 0.49</td>
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</table>

Change is calculated as the scores at or after intervention minus the scores at baseline and is presented as mean (SD). The difference in change between groups (Δ) is calculated from the change in the pyridostigmine group minus the change in the placebo group and is presented as mean difference (95% confidence interval) and the p value of the t test.

* n = 9; † n = 12; ‡ n = 19; § n = 20; ¶ n = 23; ** n = 26; †† n = 28; †‡ n = 29; ‡‡ n = 30.
CI, confidence interval; FSS, fatigue severity scale; Max, maximum; MF, median frequency; NHPE, Nottingham health profile, category “energy”; NMT, neuromuscular transmission; PSM, pyridostigmine.
group. These findings suggest that pyridostigmine does improve muscle function to some extent. This is also supported by the significant association between the improvement in walking performance and the improvement in quadriceps strength, which was found in the pyridostigmine group but not in the placebo group.

It was expected that pyridostigmine would slow down muscle fatigability. However, no changes were found on the surface EMG during the treatment period in either of the two groups. The protocol used, with a sustained contraction at 40% of MVC (as obtained at baseline), did not induce high levels of fatigue, as was shown by the small decline in MF at baseline. This left little opportunity for improvement, and a relatively higher level of effort might have been more appropriate.

Do subjects with normal sized motor units benefit more from pyridostigmine?

It was hypothesised in advance that subjects with enlarged motor units would benefit most from pyridostigmine. Contrary to this expectation, subjects with normal sized motor units improved in walking performance, while those with enlarged motor units did not. Although this unexpected subgroup effect must be interpreted with caution, it should be realised that all quadriceps muscles were symptomatic, and all showed abnormal neuromuscular transmission. An explanation might be that the normal sized motor units were, in fact, enlarged motor units that had become reduced in size over time owing to the distal degeneration of axonal branches.

Conclusions

The result of this trial was negative, as pyridostigmine did not reduce fatigue in a selected group of subjects with post-polio myelitis syndrome who were most likely to benefit from this treatment. On the other hand, the significant effect of pyridostigmine on walking distance—together with some increase in muscle fatigability. However, no changes were found on the surface EMG during the treatment period in either of the two groups. The protocol used, with a sustained contraction at 40% of MVC (as obtained at baseline), did not induce high levels of fatigue, as was shown by the small decline in MF at baseline. This left little opportunity for improvement, and a relatively higher level of effort might have been more appropriate.

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Do subjects with normal sized motor units benefit more from pyridostigmine?

It was hypothesised in advance that subjects with enlarged motor units would benefit most from pyridostigmine. Contrary to this expectation, subjects with normal sized motor units improved in walking performance, while those with enlarged motor units did not. Although this unexpected subgroup effect must be interpreted with caution, it should be realised that all quadriceps muscles were symptomatic, and all showed abnormal neuromuscular transmission. An explanation might be that the normal sized motor units were, in fact, enlarged motor units that had become reduced in size over time owing to the distal degeneration of axonal branches.

Conclusions

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