An open-labelled clinical and electrophysiological study of 3,4 diaminopyridine in the treatment of fatigue in multiple sclerosis

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Summary
We studied the electrophysiological parameters of motor performance in eight patients with multiple sclerosis and troublesome fatigue, before and after treatment with 3,4-diaminopyridine. Symptomatic fatigue was evaluated by the Krupp Fatigue Severity Score and motor performance of adductor pollicis by transcranial magnetic stimulation, rapid voluntary movements and a fatiguing exercise test of a sustained 45-s isometric contraction. The motor tests revealed baseline abnormal motor function and substantial central fatigue. After a 3-week course of 3,4-diaminopyridine (25–60 mg/day), six out of the eight patients reported substantial improvement in fatigue and the group showed slightly less fatigue on the exercise test. Other electrophysiological tests of motor function were unchanged. The findings suggest that 3,4-diaminopyridine may play a role in the symptomatic treatment of fatigue in multiple sclerosis. However, the mechanism behind such a benefit in fatigue remains unclear and the discrepancy between subjective and more objective responses underlines the probable multifactorial nature of the pathogenesis of this symptom in multiple sclerosis.

Keywords: multiple sclerosis; fatigue; amino pyridines; K⁺ channel blocker; conduction block

Abbreviations: CMCT = central motor conduction time; 3,4-DAP = 3,4-diaminopyridine; EDSS = expanded disability status scale; FSS = Fatigue Severity Scale; MEP = motor evoked potential; MVC = maximal voluntary isometric contraction; RVT = rapid voluntary twitch; TCMS = transcranial magnetic stimulation (of the motor cortex)

Introduction
The vast majority of patients with multiple sclerosis suffer from fatigue and as many as 40% describe it as their worst symptom (Murray, 1985). Although fatigue is long recognized as a symptom of multiple sclerosis (Krupp et al., 1988) there is still no effective treatment. However, some medications such as amantadine (Murray, 1985; Canadian Multiple Sclerosis Research Group, 1987; Cohen and Fisher, 1989) and pemoline (Weinshenker et al., 1992) have shown promise.

The lack of effective treatment may, in part, reflect the lack of a specific clinical definition of fatigue (Djaldetti et al., 1996) and that its mechanisms are poorly understood. Although neurological deficits in multiple sclerosis may be due to neuronal and axonal loss, some evidence suggests that they may also have a functional or physiological basis and as such would be potentially amenable to therapy. Clinically, there may be marked day-to-day and heat-dependent fluctuations. Experimentally, manipulation of body temperature (Watson, 1959) and serum ionized calcium (Davis et al., 1970) can improve symptoms. Thus, the fatigue in multiple sclerosis might be contributed to, in part, by a temporary, exercise-induced weakness due to functional or physiological blockade of conduction in central motor pathways. One possible mechanism is frequency-dependent conduction block, whereby demyelinated fibres fail to conduct the high-frequency trains of descending impulses (McDonald and Sears, 1970), as would be required in the central motor pathways during strenuous activity such as a maximal voluntary contraction. Frequency-dependent conduction block has been suggested as a mechanism of similar symptoms in multiple sclerosis, such as visual fading (Davis, 1972). Our earlier study (Sheean et al., 1997) suggested an element of centrally originating physiological fatigue (exercise-induced weakness) in the symptom, but did not support a role for frequency-dependent conduction block. However, we could
only satisfactorily examine this in the fast-conducting motor pathways. If, as we suspect, central fatigue in multiple sclerosis arises in areas driving the primary motor cortex, frequency-dependent conduction block could still be involved there, or in other tracts that modulate function of these areas, such as the sensory or (possibly) cerebellar pathways.

The hypothesis of frequency-dependent conduction block as the pathophysiological basis of fatigue in multiple sclerosis was attractive for several reasons. It would explain several clinical aspects of fatigue; the close relationship that fatigue appears to have with the clinical activity of the disease (Freal et al., 1984; Geisser, 1985), the marked temperature dependence of the symptom (Krupp et al., 1988) and the rapid development of, and recovery from, fatigue reported by some patients. However, of more important therapeutic interest is that impulse conduction in demyelinated nerves has been shown experimentally to improve with the aminopyridine group of drugs (Sherratt et al., 1980; Bostock et al., 1981; Targ and Kocsis, 1985). Aminopyridines are potassium channel blockers that prolong the duration of the action potential and improve the safety factor of nerve transmission (Bostock et al., 1981). Thus, they might prove therapeutically beneficial for fatigue as they have for other symptoms in multiple sclerosis. Trials of both of the available aminopyridines, 3,4-diaminopyridine (3,4-DAP) (Bever et al., 1990; Carter et al., 1993) and 4-aminopyridine (Jones et al., 1983; Stefoski et al., 1987, 1991; Davies et al., 1990; van Diemen et al., 1992; Bever et al., 1994; Polman et al., 1994a, b), have shown benefit for many neurological symptoms in multiple sclerosis, including weakness (Bever et al., 1996) and fatigue (Polman et al., 1994a, b). A review of the literature on the use of aminopyridines in multiple sclerosis has been given by Bever (1994).

Although clinical benefit in some neurological symptoms with aminopyridine treatment has been demonstrated, there has been little accompanying electrophysiological evaluation of CNS function. Improvement in visual evoked potential latencies (Bever et al., 1990; van Diemen et al., 1993; Polman et al., 1994b) and contrast sensitivity (Bever et al., 1994; Polman et al., 1994b) has been noted. Having developed a tool with which to measure the physiological component of central fatigue of multiple sclerosis, we were interested to see if aminopyridine treatment could improve central fatigue or other electrophysiological tests of central motor function, and then to relate this to any subjective improvement in fatigue.

Patients and methods

Eight patients with clinically definite multiple sclerosis (Poser et al., 1983) and complaining of fatigue were recruited. All (four male and four female) had participated in a previous study of fatigue in multiple sclerosis (Sheean et al., 1997). The degree of symptomatic fatigue reported by the patients was scored using the self-administered Fatigue Severity Scale (FSS) developed and validated by Krupp et al. (1989). The FSS was repeated at the completion of the treatment period. Neurological disability was evaluated with the Kurtzke expanded disability status scale (EDSS) at entry into the study only. Heat sensitivity of fatigue was graded on a seven-point scale (1 = no or minimal sensitivity; 7 = marked sensitivity). Because aminopyridines are potentially epileptogenic (Bever et al., 1994; Bever et al., 1996; Polman et al., 1994b), patients were excluded if there was a history of seizures, or of unexplained loss of consciousness, or if an EEG showed significant abnormalities. Baseline electrophysiological test results prior to receiving 3,4-DAP were compared with those obtained from a group of 19 normal subjects, comprising eight males and 11 females, ranging in age from 22 to 40 years (mean 31.9 years).

Baseline electrophysiological tests

All tests were performed on the right adductor pollicis muscle and have been described in detail elsewhere (Sheean et al., 1997). The subject’s hand was placed in a custom-built myograph which registered force of isometric contractions of adductor pollicis. Compound muscle action potentials were recorded from the adductor pollicis with 9-mm silver–silver chloride disk electrodes (placed on the muscle belly and tendon) and amplified using D190 amplifiers with a low pass filter of 3 kHz and a time constant of 100 ms. Force output was amplified separately through a bandpass of DC to 400 Hz. Force resolution was 0.03 kg. All data were passed through a CED1401 analogue-to-digital converter with a sampling frequency of 1000 Hz, and stored on a personal computer for later analysis.

Central motor conduction was assessed by transcranial magnetic stimulation (TCMS) of the motor cortex by a Digitimer D150 (Digitimer, Welwyn Garden City, Herts., UK) using a circular coil (inner diameter 10 cm) placed at the vertex. Shocks were delivered during a small contraction (~5–10% of maximal) of the adductor pollicis with a stimulus intensity of 120% of resting threshold. Resting threshold was determined to the nearest 2.5% of stimulator output, according to previously described methods (Kujirai et al., 1993). Central motor conduction time (CMCT) was calculated from F- and M-wave latencies (Murray, 1992) obtained from supramaximal electrical stimulation of the ulnar nerve at the wrist. The area and peak-to-peak amplitude of the motor evoked potential (MEP) produced in response to TCMS were expressed as ratios of the M-wave size.

Performance of rapid voluntary movements depends upon the rapid recruitment of motor units and may be impaired in multiple sclerosis (van der Kamp et al., 1991). With the hand in the myograph, patients performed individually rapid, isometric adduction movements of the thumb. After a short practice and a period of rest, several rapid voluntary twitches (RVTs) were recorded. The best of the first three relatively reproducible RVTs was analysed. The maximum rate of rise of force was determined by force differentiation and normalized to the peak force produced (Miller et al., 1993).
Fatigue in multiple sclerosis

Baseline strength was measured by the patient performing a maximal voluntary isometric contraction (MVC) of the adductor pollicis for several seconds. The level of central motor drive (central activation) was measured by the twitch interpolation technique (Lloyd et al., 1991) involving paired supramaximal electric stimuli given to the ulnar nerve (Sheean et al., 1997). Central activation was calculated from the formula: central activation (%) = [1 – (force increment/stimulated twitch force)]×100, where force increment (kg) is the amount of extra force produced from paired supramaximal ulnar nerve stimulation during MVC, and stimulated twitch force (kg) is that evoked by the same paired stimulus at rest after the MVC (Lloyd et al., 1991).

**Fatiguing exercise test**

To induce fatigue, the subjects performed 45 s of sustained MVC of the adductor pollicis during which force was recorded. The patients were naive, in that they had not previously performed the exercise test. During the exercise, they were loudly exhorted to maintain full effort throughout and visual feedback was given from a nearby oscilloscope displaying force output. Force and central activation was measured every 3 s during the sustained MVC; force was expressed as a ratio of the pre-exercise maximum voluntary force. Physiological fatigue was quantified by the force and central activation produced at the end of the test and by the area under the force-time curve expressed as a ratio of the theoretical maximum subtracted from 100% (Djaldetti et al., 1996) (see Fig. 1). The latter we labelled the ‘physiological fatigue index’. At the end of the exercise, three further paired electrical stimuli were given at rest, 1.5 s apart, to measure twitch force. The baseline tests of RVTs and MEP measurements were then repeated as quickly as possible, beginning within 10 s of completion of the exercise. The first RVT after exercise was analysed to observe the maximal effect.

**3,4-DAP**

At the end of the above protocol, an oral test dose of 20 mg of 3,4-DAP was given and the protocol repeated 1 h later, coinciding with the expected peak blood concentrations of 3,4-DAP (Bever et al., 1990). If no serious side effects arose, each patient was prescribed either 50 or 60 mg/day in three divided doses, according to body size, taken for 3 weeks. At the end of the 3-week treatment period, the test protocol was repeated; the FSS was re-administered and the patients were also asked to provide a global subjective assessment of any change in their fatigue on a nine-point scale (where 0 = no change and 1, 2, 3 and 4 represent slight, mild, moderate, and substantial improvement or deterioration). The follow-up tests were performed at the same time of day as the baseline tests and the room temperature was constant.

**Statistical analysis**

Comparisons of data obtained before and after the exercise test and before and after treatment with 3,4-DAP were made using the paired t test or the Wilcoxon rank sum test. Analysis was also performed using MANOVA. Values of P < 0.05 were considered significant. Results are presented as mean ± standard deviation. The Spearman rank correlation

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**Fig. 1** Force output from fatiguing exercise test in Patient 3 before and after a 3-week course of 3,4-DAP. Shaded area represents loss of force production (fatigue), quantified as the physiological fatigue index. Note reduction in fatigue after 3,4-DAP; the physiological fatigue index decreased from 29.2% to 21%. At the end of the exercise, central activation was 53.2% before and 68% after 3,4-DAP.
Fig. 2 MEPs and rapid voluntary movements prior to the fatiguing exercise (i.e. at rest) before and after 3,4-DAP for Patient 3 (the same patient as illustrated in Fig. 1). Note similarity of results in the two states. The post-exercise responses were also similar in the two states.

Table 1 Clinical characteristics of patients*

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Disease duration (years)</th>
<th>Type†</th>
<th>EDSS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>37</td>
<td>F</td>
<td>2</td>
<td>Relapsing–remitting</td>
<td>2.0</td>
</tr>
<tr>
<td>2</td>
<td>50</td>
<td>M</td>
<td>7</td>
<td>Relapsing–remitting</td>
<td>6.0</td>
</tr>
<tr>
<td>3</td>
<td>46</td>
<td>M</td>
<td>22</td>
<td>Secondary progressive</td>
<td>6.0</td>
</tr>
<tr>
<td>4</td>
<td>44</td>
<td>M</td>
<td>10</td>
<td>Primary progressive</td>
<td>6.5</td>
</tr>
<tr>
<td>5</td>
<td>34</td>
<td>M</td>
<td>13</td>
<td>Relapsing–remitting</td>
<td>8.0</td>
</tr>
<tr>
<td>6</td>
<td>39</td>
<td>F</td>
<td>20</td>
<td>Secondary progressive</td>
<td>7.0</td>
</tr>
<tr>
<td>7</td>
<td>26</td>
<td>F</td>
<td>7</td>
<td>Relapsing–remitting</td>
<td>6.5</td>
</tr>
<tr>
<td>8</td>
<td>34</td>
<td>F</td>
<td>6</td>
<td>Relapsing–remitting</td>
<td>6.0</td>
</tr>
<tr>
<td>Mean</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>6.0</td>
</tr>
</tbody>
</table>

EDSS = expanded disability status scale. *All patients had clinically definite multiple sclerosis according to Poser criteria (Poser et al., 1983). †Refers to clinical type at the time of testing.

Results

Pre-3,4-DAP

Clinical results

The clinical characteristics of the patients are given in Tables 1 and 2. The mean duration of disease was 10.8 ± 7.1 years. The mean EDSS (Kurtzke, 1983) score was 6, showing that the patients were moderately to severely disabled neurologically. However, this disability was largely confined to the lower limbs; the upper limbs being relatively spared as shown in the measurements of strength below (see results of baseline motor function below). The mean FSS score was 5.5 (normal range <4.0; Krupp et al., 1989). Six patients described their fatigue as markedly heat-sensitive.

Electrophysiological results

Baseline motor function. CMCT in the patient group was markedly prolonged; mean CMCT was 10.9 ± 5.4 ms compared with 4.4 ± 0.9 ms in the control subjects. Mean MEP area and amplitude (as percentages of M-wave values) were 40.7 ± 21.2% and 23.9 ± 14%, respectively. The mean baseline-normalized peak rate of force rise during a RVT was 9.2 ± 2.5 for patients compared with the control value of 14.2 ± 3.1. M-wave size was similar in the two groups. MVC force at baseline was 4.35 ± 1.0 kg in the patients, which was not significantly different from that of the control subjects (5.0 ± 1.2 kg). Baseline central activation was likewise similar to that of control subjects; 94.1 ± 5.4% versus 97.2 ± 4.1% for the control subjects. Stimulated (electrical) twitch force was similar in the two groups at baseline.

In summary, the patients had dysfunction of the central...
motor pathways as evidenced by prolonged CMCTs and slowness of rapid voluntary movements, but they had unimpaired strength in the target muscle.

**Exercise test.** After 45 s of MVC, the force had declined to 59.9 ± 23.7% of baseline maximum ($P < 0.02$) in the patients. Central activation fell from 94.1 ± 5.4% to 56.5 ± 29.3% ($P < 0.05$) indicating a substantial degree of central fatigue. The end of exercise values for force and central activation in the control group were 82.0 ± 14.5% and 90.6 ± 13.0%, respectively. The changes in force output and central activation in the patients were significantly different (greater) compared with the control subjects ($P < 0.05$). The mean physiological fatigue index was 30.6 ± 16% in the patients but was not calculated for the control group. After exercise, the electrical twitch force, which had been similar in the two groups prior to exercise, was reduced in the control group ($P < 0.05$), consistent with the development of peripheral fatigue, but unchanged in the patient group. Thus, the patients demonstrated a large amount of fatigue which was central in origin whereas the control subjects fatigued only moderately and this appeared to be peripheral in origin (see Sheean et al., 1997). RVT performance was significantly slowed by the exercise test in each group ($P < 0.05$) but to a similar degree. There were no significant changes in CMCT, MEP size or M-wave size after exercise in either the patient or control groups.

**Post-3,4-DAP**

**Clinical results (Table 2)**

At the end of the 3-week trial of 3,4-DAP, six patients reported improvement in their fatigue, all moderate or substantial in degree, whilst two patients reported no overall improvement. In one of these two (Patient 5), the only change was a marked improvement in the heat sensitivity of his fatigue. Those reporting improvement in fatigue also reported a noticeable reduction in the heat sensitivity of the fatigue. Thus, only four patients reported improvement in heat sensitivity of fatigue, perhaps because the study was carried out in the colder months of the year. The mean FSS score of the group fell from 5.5 to 3.7 ($P < 0.01$).

Side effects, notably paraesthesiae, were reported by six patients (Table 2), necessitating a dose reduction in three (all female). These dose reductions (in all subjects a halving of the dose) occurred within a few days of beginning the medication and resulted in a marked improvement of the side-effects to tolerable levels. No seizures occurred.

**Electrophysiological results (Table 3)**

The electrophysiological data, including those from the exercise test, performed 1 h after the single 20 mg test dose of 3,4-DAP, were unchanged and will not be considered further.

**Pre-exercise motor function.** At the end of 3 weeks of treatment with 3,4-DAP, there were no significant changes in the group means of pre-exercise M-wave size, CMCT, MEP size, RVT performance or MVC force compared with values before treatment with 3,4-DAP (Fig. 2). One patient showed a mild increase in baseline strength (Fig. 1). Central activation ($P < 0.05$) and electrical twitch force ($P < 0.02$) were slightly greater after treatment with 3,4-DAP. Resting and facilitated TCMS thresholds remained unchanged.

**Exercise test.** Two of the fatigue parameters, the mean force and central activation at the end of exercise, were not significantly different from those before treatment with 3,4-DAP. However, the physiological fatigue index showed a significant increase after treatment with 3,4-DAP ($P < 0.05$; Fig. 1) indicating reduced fatigue. There was still no change in post-exercise CMCT, MEP size or M-wave size after 3,4-DAP treatment, despite central fatigue. RVT performance was still slowed by exercise but to the same degree as before 3,4-DAP treatment. Following 3,4-DAP treatment, the electrical twitch force fell slightly after exercise ($P < 0.05$, Wilcoxon), suggesting a small degree of peripheral fatigue that had not been present before 3,4-DAP.

**Clinical–electrophysiological correlations**

Before receiving 3,4-DAP, the baseline FSS score was correlated ($P < 0.01$) with the degree of central fatigue (as assessed by the change in central activation) evoked by the exercise test. Those with slower RVT performance developed greater fatigue ($P < 0.02$) but there was no correlation between physiological fatigue and TCMS parameters of CMCT or MEP size. Subjective change in fatigue after 3,4-DAP was measured by the FSS and by a simpler subjective rating (see Patients and methods). Correlations were found between the baseline FSS score and the reduction in FSS score after 3,4-DAP ($P < 0.05$); the higher the baseline FSS score, the greater was the reported improvement in fatigue. The reduction in FSS score also correlated with the global subjective improvement in fatigue ($P < 0.05$). There were no significant correlations between other clinical parameters (EDSS, disease duration, age or heat sensitivity) and subjective change in fatigue. Similarly, the pre-exercise electrophysiological parameters (RVT performance, CMCT and MEP size) and the baseline degree of central fatigue were not correlated with the subjective improvement.

**Correlations with change in electrophysiological parameters after 3,4-DAP**

There was a significant improvement in physiological fatigue as measured by the physiological fatigue index following treatment with 3,4-DAP. This change was correlated with only one of the pre-treatment clinical factors, the baseline FSS score ($P < 0.02$); the more severe the symptom of fatigue before treatment, the greater was the improvement in physiological
## Table 2: Clinical response to 3,4-DAP

<table>
<thead>
<tr>
<th>Patient</th>
<th>Dose of 3,4-DAP*</th>
<th>FSS (pre-)</th>
<th>FSS (post-)</th>
<th>Heat (pre-)</th>
<th>Heat (post-)</th>
<th>Subjective response</th>
<th>Side-effects</th>
<th>Other clinical changes</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>60 mg</td>
<td>5.4</td>
<td>4.3</td>
<td>7</td>
<td>4</td>
<td>+3</td>
<td>Cramps, funny taste in mouth</td>
<td>Gait more steady</td>
</tr>
<tr>
<td>2</td>
<td>60 mg</td>
<td>6.7</td>
<td>4.1</td>
<td>7</td>
<td>4</td>
<td>+3</td>
<td>None</td>
<td>Improved bladder control, less physical and mental fatigue</td>
</tr>
<tr>
<td>3</td>
<td>60 mg</td>
<td>5.8</td>
<td>2.3</td>
<td>7</td>
<td>4</td>
<td>+4</td>
<td>Peri-oral paraesthesiae</td>
<td>Gait steadier, increased strength, improved bladder control, improved co-ordination and sensation in hands</td>
</tr>
<tr>
<td>4</td>
<td>60 mg</td>
<td>5.6</td>
<td>3.3</td>
<td>4</td>
<td>4</td>
<td>+4</td>
<td>Paraesthesiae (acral, peri-oral), insomnia, loss of taste sensation, abdominal cramps</td>
<td>Gait more steady</td>
</tr>
<tr>
<td>5</td>
<td>60 mg</td>
<td>5.4</td>
<td>5.8</td>
<td>7</td>
<td>5</td>
<td>0</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>6</td>
<td>50 mg</td>
<td>6.6</td>
<td>4.2</td>
<td>7</td>
<td>7</td>
<td>+4</td>
<td>Paraesthesiae (acral, peri-oral), light-headed</td>
<td>Less physical and mental fatigue</td>
</tr>
<tr>
<td>7</td>
<td>50 mg</td>
<td>5.6</td>
<td>2.4</td>
<td>4</td>
<td>4</td>
<td>+4</td>
<td>Paraesthesiae (acral, peri-oral)</td>
<td>Improved balance (gait) and reduced back pain</td>
</tr>
<tr>
<td>8</td>
<td>50 mg</td>
<td>2.7</td>
<td>2.8</td>
<td>7</td>
<td>7</td>
<td>0</td>
<td>Paraesthesiae (acral, peri-oral) tight band around trunk, 'cold' feeling inside</td>
<td>None</td>
</tr>
</tbody>
</table>

*Dose in parentheses is that taken after reduction necessitated by side-effects. FSS = Fatigue Severity Scale score (list of nine items scored 1 to 7). Heat = heat sensitivity of fatigue scored from 1 (no heat sensitivity) to 7 (strongly heat sensitive). Subjective response scale: 0 = no change; 1, 2, 3 and 4 represent slight, mild, moderate and substantial change; + = improvement and – = deterioration.
fatigue. However, the amount of physiological fatigue present before 3,4-DAP, as measured by the more objective exercise test, was not correlated with the degree of improvement after 3,4-DAP. Of the baseline (pre-exercise, pre-3,4-DAP) electrophysiological parameters, only RVT performance was correlated (inversely) with improvement in physiological fatigue post-3,4-DAP (physiological fatigue index, \( P < 0.05 \)). Those with slower RVT performance at baseline (before exercise and 3,4-DAP) showed greater improvement in physiological fatigue after 3,4-DAP. None of the subjective measures of response (the reduction in FSS score or subjective score) was correlated with any measure of physiological improvement.

In summary, the only predictor of a subjective improvement in fatigue with 3,4-DAP was the baseline FSS score. Improvement in physiological fatigue (the exercise test) was predicted by one subjective parameter, the baseline FSS score, and one objective parameter, baseline RVT performance; improved physiological fatigue after 3,4-DAP was not predicted by the degree of baseline physiological fatigue. Most importantly, no correlation was found between subjective improvement in fatigue and improvement in physiological fatigue and there was a substantial discrepancy in the magnitude of the change in these two parameters.

**Discussion**

In this group of patients with clinically-define multiple sclerosis and severe symptomatic fatigue, excessive central physiological fatigue was demonstrated. Treatment with 3,4-DAP for 3 weeks resulted in marked subjective improvement of fatigue in six of the eight patients. This was accompanied by a slight but definite improvement in performance of the exercise test, that is, reduced physiological fatigue (fatigue index). This apparent improvement in fatigue occurred without any improvement in central motor conduction or in other measures of motor function (e.g. rapid voluntary movements). It should be acknowledged that the change in the fatigue index had a \( P \)-value of just <0.05. This, and the fact that several statistical comparisons were performed on the data, could diminish the significance of the result.

The striking finding of our study is the large discrepancy between the magnitude of subjective improvement in fatigue and the degree of improvement in central physiological fatigue, with no statistical correlation between the two. These patients were part of a larger group in whom we had shown that the degree of exercise-induced central fatigue did not correlate with the severity of the symptom of fatigue (Sheean et al., 1997). Therefore, symptomatic improvement might not be expected to accompany improvement in physiological fatigue. Another possible explanation concerns the use of the upper limb for physiological testing. A large part of the overall sensation of fatigue may come from fatigue in the lower limbs. Thus, lower limb testing, although technically more difficult, might have shown a better correlation with the baseline global subjective assessment of fatigue (FSS score) and possibly a greater and proportional improvement in physiological fatigue after 3,4-DAP. Finally, the dose of 3,4-DAP used in the study may have been too small to produce a substantial physiological change. We had been deliberately cautious so as to minimize the risk of seizures but despite this several of our patients (all female) required a dose-reduction because of side-effects. It should be noted, however, that Bever et al. (1996) found no correlation between serum levels of 3,4-DAP and clinical efficacy.

An obvious limitation of this study is the lack of placebo control. Performance of the fatiguing exercise test could have been influenced by a placebo effect and the exercise test performed after 3,4-DAP was the patients’ third attempt, raising also the possibility of a learning effect. However,

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### Table 3 Electrophysiological results for patients

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Pre-3,4-DAP</th>
<th>Post-exercise</th>
<th>Post-3,4-DAP</th>
</tr>
</thead>
<tbody>
<tr>
<td>MVC (maximal voluntary contraction)</td>
<td>4.35 ± 1.00</td>
<td>6.5 ± 29.3*</td>
<td>5.9 ± 11.0</td>
</tr>
<tr>
<td>Central activation (%)</td>
<td>94.1 ± 5.4</td>
<td>10.7 ± 6.4</td>
<td>57.8 ± 12.9</td>
</tr>
<tr>
<td>Physiological fatigue index (%)</td>
<td>30.6 ± 16.0</td>
<td>40.7 ± 11.9</td>
<td>24.1 ± 17.8*</td>
</tr>
<tr>
<td>Twitch force (kg)</td>
<td>1.94 ± 0.58</td>
<td>2.17 ± 0.74**</td>
<td>1.90 ± 0.70*</td>
</tr>
<tr>
<td>RVT (maximal rate of force rise)</td>
<td>5.4 ± 1.19</td>
<td>5.2 ± 2.57</td>
<td>13.5 ± 4.2</td>
</tr>
<tr>
<td>M-wave amplitude (mV)</td>
<td>16.0 ± 6.1</td>
<td>15.3 ± 5.8</td>
<td>11.9 ± 3.8*</td>
</tr>
<tr>
<td>M-wave area (mVs)</td>
<td>0.045 ± 0.02</td>
<td>0.046 ± 0.02</td>
<td>0.043 ± 0.02</td>
</tr>
<tr>
<td>Resting TCMS threshold (%)</td>
<td>69.5 ± 6.5</td>
<td>67.0 ± 6.5</td>
<td>60.0 ± 11.2</td>
</tr>
<tr>
<td>Active TCMS threshold (%)</td>
<td>60.0 ± 13.5</td>
<td>60.0 ± 11.2</td>
<td>11.0 ± 5.2</td>
</tr>
<tr>
<td>CMCT (ms)</td>
<td>10.9 ± 5.4</td>
<td>11.1 ± 5.6</td>
<td>11.0 ± 5.9</td>
</tr>
<tr>
<td>MEP area (%)</td>
<td>40.7 ± 21.2</td>
<td>30.6 ± 16.2</td>
<td>33.7 ± 25.1</td>
</tr>
<tr>
<td>MEP amplitude (%)</td>
<td>23.9 ± 14.0</td>
<td>19.3 ± 12.9</td>
<td>16.7 ± 0.1*</td>
</tr>
</tbody>
</table>

MVC = maximal voluntary contraction; MEP = motor evoked potential—area and amplitudes are expressed as ratios (%) of the M wave; CMCT = central motor conduction time (ms); RVT = maximal rate of force rise of the rapid voluntary twitch normalized to force amplitude; Physiological fatigue index—see Patients and methods section for details. \(* P < 0.05\) and \(**P < 0.02\) for comparisons between pre- and post-3,4-DAP. \(† P < 0.05\) for comparisons between pre- and post-exercise.
of 3,4-DAP, which produced obvious side effects in most subjects. Furthermore, some of these patients performed the exercise test on another occasion, well after the 3,4-DAP trial, and showed a degree of central fatigue strikingly similar to that of the baseline (pre-3,4-DAP) test. Another test of motor performance, the RVT, showed no improvement after 3 weeks of 3,4-DAP treatment; one would have to argue that placebo or learning effects were applicable to one motor test and not the other. Finally, additional support for a true benefit comes from a placebo-controlled study that demonstrated improved fatigue with aminopyridine treatment (Polman et al., 1994b).

For these reasons we believe that the slight improvement in physiological fatigue was not due to a placebo or learning effect.

The discrepancy between the subjective and objective benefits underlines the fact that physiological fatigue is only one component of the symptom of fatigue, and it raises the question of the mechanism by which 3,4-DAP improved fatigue. The experimentally proven ability of 3,4-DAP to improve conduction in demyelinated nerves would seem the most likely explanation for the slight improvement in physiological fatigue. Indeed, patients with the slowest RVT performance showed the greatest physiological fatigue beforehand and the most improvement in exercise test performance after 3,4-DAP. However, the arguments against this explanation are that treatment with 3,4-DAP did not produce improvement in RVT performance, before or after exercise, or in conduction in the primary, large diameter, central motor pathways, as assessed by TCMS. Thus, the mechanism of physiological benefit appears not to involve these pathways. If on the other hand, 3,4-DAP was acting to enhance drive to the primary motor cortex, a deficiency of which may underlie the physiological fatigue in multiple sclerosis (Sheean et al., 1997), then one might have expected a change in RVT performance, which would also be expected to depend upon intact drive to the primary motor cortex.

Alternatively, as aminopyridines are known to be epileptogenic (Bever et al., 1994; Polman et al., 1994b; Bever et al., 1996), 3,4-DAP may simply exert a non-specific central stimulant effect, which could explain the discrepancy between the subjective and physiological improvements in fatigue. Synaptic mechanisms similar to those mediating enhanced acetylcholine release at neuromuscular junctions in Lambert–Eaton myasthenic syndrome (Murray and Newsom-Davis, 1981) could be involved. Although only a rough indicator of cortical excitability, TCMS thresholds were unchanged after 3,4-DAP. A further complication is that, while the patients mostly reported that the benefits began and subsided within 1 week of commencement and cessation of treatment, some reported continuing improvement for 2–3 weeks after cessation; this is difficult to explain given the short half-life of 3,4-DAP (Bever et al., 1990).

It has been suggested that patients whose multiple sclerosis symptoms are heat-sensitive show the best response to aminopyridines (van Diemen et al., 1992). Both the fatigue of multiple sclerosis (Krupp et al., 1988) and the conduction abnormalities in demyelinated nerves are temperature sensitive (Davis and Jacobsen, 1971; Rasminsky, 1973), and aminopyridines raise the critical temperature at which conduction block occurs (Bostock et al., 1981).

Disappointingly, in this study, neither the degree of baseline heat-sensitivity nor the change in heat-sensitivity after 3,4-DAP was correlated with improved subjective or physiological fatigue. This may not be surprising given that most patients were strongly heat-sensitive.

Side-effects were common and dose-limiting in several patients (all female). Despite this, five of the six patients who benefitted expressed the desire to continue the medication.

This study suggests a potential role for 3,4-DAP in the symptomatic treatment of fatigue in multiple sclerosis, in accordance with the findings of other researchers (Polman et al., 1994a, b). Those with the greatest subjective fatigue seem to have the greatest subjective response, but there were no other factors predictive of this; specifically, none of the electrophysiological measures of motor function. Although some subjective and objective factors were predictive of improved physiological fatigue, this objective response was relatively small compared with the magnitude of the subjective response. Thus, electrophysiological tests of motor function and fatigue appear to be unhelpful in the clinical management of the individual patient. However, they may play a role in therapeutic studies by providing some degree of objective validation. The mechanism of benefit of 3,4-DAP in fatigue remains unclear but seems to depend very little on improved motor performance. The slight improvement in physiological fatigue at least supports the notion that aminopyridines may work in vivo to improve conduction in demyelinated central pathways, but direct evidence of this is lacking. Further placebo-controlled electrophysiological and clinical studies are required to establish the role of aminopyridines in the symptomatic treatment of fatigue in multiple sclerosis.

References


Fatigue in multiple sclerosis


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