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EFFECTS OF 4-AMINOPYRIDINE IN PATIENTS WITH MULTIPLE SCLEROSIS

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SUMMARY

4-Aminopyridine (4-AP) was administered to two groups of patients with multiple sclerosis (MS). The first group consisted of 5 patients with labile visual symptoms, 2 of whom had arcuate scotomata. 4-AP improved visual performance of most patients in this group and reduced the size of scotomata. The second group consisted of 5 patients with the spinal form of MS who were in a stable state; in this group 4-AP had little effect clinically or on tests of visual function.

Key words: *4-Aminopyridine – Conduction factors – Multiple Sclerosis – Psychophysical measurement*

INTRODUCTION

Demyelination of central or peripheral myelinated nerve fibres may cause delay in conduction, intermittent conduction block and increase in refractory period, leading to an inability to transmit fast trains of impulses (McDonald and Sears 1970). Abnormalities in transmission in affected nerve fibres may be labile, and can be influenced by temperature or metabolic factors. For example,

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an increase in body temperature may increase the size of scotomata, reduce visual acuity (Namerow 1968), lower critical flicker frequency (Namerow 1971), and cause a deterioration in motor signs (Davis 1966). Conversely, lowering body temperature may improve visual and motor function (Watson 1959). Reduction in the ionised serum calcium may also enhance transmission, and it has been shown that intravenous sodium bicarbonate and disodium edetate reduce the size of scotomata and decrease the frequency of nystagmus in some patients with MS (Davis et al. 1970).

We have previously reported from this laboratory that the changes in conduction characteristics that occur under such labile conditions can be monitored by measuring temporal resolution of vision (Galvin et al. 1976). It has also been shown that visual evoked potentials (VEPs) are sensitive to changes in conduction characteristics. Persson and Sachs (1981) reported that the amplitude of the major positive component diminished on exercise in patients with MS and Uhthoff's sign, and returned to its former value after exercise.

Since neither change in body temperature nor changes in calcium-ion concentration offer a practical means of therapy, recent interest in factors influencing conduction defects in MS have led to an attempt to modify conduction favourably by the use of drugs. Sherratt et al. (1980) have shown that 4-aminopyridine (4-AP), a drug that blocks potassium channels in the axon membrane, prolongs the action potential in experimentally demyelinated rat nerve and overcomes conduction block.

4-AP has previously been used with effect in the treatment of myasthenia gravis (Lundh et al. 1979) and the Eaton–Lambert syndrome (Lundh et al. 1977). In view of the experimental results of Sherratt et al. (1980) we assessed the effect of the drug in patients with MS.

We examined two groups of patients with MS. The first group consisted of patients who had labile visual symptoms, since we expected that any beneficial effect of the drug might be more readily apparent in this group. The second group consisted of patients with MS and spastic paraparesis (spinal MS) who were in a stable state. The effects of 4-AP in these two groups were assessed clinically and by tests of visual function. The effects of 4-AP on visual function in two normal subjects were also evaluated in a preliminary experiment.

PATIENTS

Group 1

This consisted of 5 patients with MS and a history of optic neuritis (ON). All had labile visual symptoms influenced by temperature or exercise (see Table 1). Two of the patients in this group (SC, DW) had arcuate scotomata on perimetry.

Group 2

This consisted of 5 patients with the spinal form of MS who were in a clinically stable state (see Table 2). Four of the 5 patients had optic atrophy.

TABLE 1

DETAILS OF GROUP 1 PATIENTS (HISTORY OF OPTIC NEURITIS) WITH LABILE SYMPTOMS

Patient	Age (yr)	Duration disease (yr)	Previous optic neuritis[a]	Labile symptoms	Clinical diagnosis
SB	29	6	L + R	Transient loss of vision; gaps in vision paroxysmal dysarthria	Definite MS
LH	33	2.5	R	Recurrent transient blurring of vision	Definite MS
SC	31	1	L	Transient mosaic patterns in left eye on neck flexion and Lhermitte's sign	Definite MS
DW	46	1.5	R	Blurring of vision on neck flexion, warm baths, walking uphill	Definite MS
SH	29	4	L	Blurred vision when fatigued or with exercise	Definite MS

[a] L = left eye, R = right eye.

TABLE 2

DETAILS OF GROUP 2 PATIENTS (SPINAL MS, STABLE)

Patient	Age (yr)	Duration disease (yr)	Time since last relapse (yr)	Clinical state	Clinical diagnosis
JL	35	10	3	Spastic paraparesis Cerebellar signs (slowly progressive) Optic neuropathy	Definite MS
JH	44	14	2	Spastic paraparesis Cerebellar signs (static) Optic neuropathy	Definite MS
ML	56	2.5	2	Spastic paraparesis Cerebellar signs (slowly progressive)	Definite MS
JB	43	9	1 (ON)	Spastic paraparesis Optic neuropathy (static)	Definite MS
WW	71	12	12	Spastic paraparesis (progressive) Optic neuropathy	Definite MS

Informed consent was obtained from all patients. Ethical permission was granted by the Ethical Committee of the North Staffordshire Hospital Centre.

APPARATUS

Measurements of luminance threshold and temporal resolution of vision were made using a modified visual perimeter which allowed the presentation of small, circular stimuli at various locations within a circular visual field subtending 20° at the eye. Stimuli were produced by light-emitting diodes (LEDs) (Monsanto MV5752, peak emission wavelength 630 nm); these were driven by suitable electronics which controlled the intensity and time course of the flashes. Angle of subtense was 10 min arc. For measurement of luminance threshold, a single flash, duration fixed at 20 ms, was presented with variable intensity. For measurement of temporal resolution, two flashes with variable onset delay were presented at the same site, each flash 20 ms duration and luminance 3.7 log $cd.m^{-2}$. The stimulus field was viewed through an optical system that provided a constant, spatially uniform white background field (luminance 2.2 log $cd.m^{-2}$, colour temperature 3060°K) upon which the stimuli appeared superimposed. Stimuli were presented foveally or at a peripheral retinal site in a quadrant containing a scotoma. The peripheral retinal site was situated at an eccentricity of 2.5° and azimuth of 45° relative to the horizontal.

VEPs were recorded to 12, 24, and 48 min-arc check sizes using monocular stimulation. Stimuli were generated by a Medelec visual stimulator and the results analysed by a Datalab 4000 microprocessor.

PROCEDURE

In a preliminary session, patients' visual acuity was assessed using Snellen and Faculty of Ophthalmologists' test type. Visual fields were plotted on a tangent screen.

For the measurement of luminance threshold and temporal resolution, subjects were seated in a chair, with a firm headrest, at a distance of 1.7 m from the screen; spectacles were worn if appropriate and the eye not being tested was occluded. Subjects fixated a target in the centre of the screen and controlled the onset of the stimulus by means of a push-button switch.

In determining luminance threshold, an approximate value was first obtained by a method of limits. Ten consecutive intensity settings at 0.1-log-unit intervals were then selected with the approximate threshold value in the middle of the range. Flashes of these intensities were presented in random order. After a rest period of approximately 30 s, the 10 flashes were again presented, in a different order, and this procedure repeated until each flash at each intensity had been presented 5 times in all. The randomization of the intensities in each sequence was chosen according to a design that minimized order and carry-over effects.

The assessment of temporal resolution of vision was performed by measuring

the time interval by which two pulses of light had to be separated in order to be seen as double. Stimuli were presented in random order, as for the determination of luminance threshold.

Protocol for Group 1 (labile visual symptoms)

Base-line measurements of luminance threshold and temporal resolution were recorded. Subjects were then given orally 10 mg of a lactose placebo, and the two visual measurements were repeated after periods of approximately 1, 2 and 3 h. Subjects were then given 20 mg of a lactose placebo and the visual measurements repeated after approximately 1, 2 and 3 h.

On a separate day, the experiment was repeated under identical laboratory conditions. Subjects were given orally 10 mg of 4-AP sulphate. Visual measurements were recorded at the same time intervals as for the placebo. Providing this dose of 4-AP was tolerated, subjects were given 20 mg of 4-AP sulphate and the visual measurements again repeated as for the placebo.

In the two patients with consistently reproducible arcuate scotomata the size of the scotomata was monitored during the course of the experiment.

The experiment was not performed double blind, for in our preliminary experiments with normal subjects the induced stereotyped side-effects made it obvious which capsules contained the active drug. The ordering of sessions with placebo and 4-AP was chosen at random.

The effect of 4-AP on VEPs was also assessed in two subjects in Group 1 (patients SH and DW; Table 1). VEPs were recorded before treatment. The two subjects were then given 60 mg of 4-AP sulphate daily for a week; one patient (SH) was unable to tolerate this dose, which was reduced to 20 mg daily. After 7 days of treatment, VEPs were recorded again.

Protocol for Group 2 (spinal MS)

Initial clinical assessment was performed using the Kurtzke scale (Kurtzke 1961). Baseline measurements of luminance threshold and temporal resolution were recorded. Subjects were then given orally 60 mg of a lactose placebo daily for 7 days. At the end of that time they were reassessed clinically and visual measurements repeated.

They were then given orally 60 mg of 4-AP sulphate daily for 7 days. Two of the 5 patients could not tolerate this dose which was therefore reduced to 20 mg daily. After 7 days of treatment they were again assessed clinically and visual measurements repeated. The experiments were not performed double-blind for the reasons stated previously.

DATA ANALYSIS

Data derived from the visual measurements of luminance threshold and temporal resolution were analysed by probit analysis (Finney 1952). This allowed an estimate to be made of both the threshold and the variability of that threshold

(Patterson et al. 1980). (The underlying normal distribution assumed by probit analysis was not intended to have any theoretical significance here.) Data values were then normalized with respect to baseline values.

RESULTS

Group 1

The results obtained from patients in Group 1 (labile visual symptoms) are summarized in Table 3. The quantities tabulated are mean increases in luminance threshold, variability in luminance threshold, temporal resolution, and variability in temporal resolution for 4-AP relative to placebo. Positive values indicate an improvement in that parameter.

Of the 20 values obtained, 70% showed an improvement following the administration of 4-AP, which was significant ($P < 0.05$). In one patient (SH) there was a significant improvement in luminance threshold ($P < 0.05$), variability of luminance threshold ($P < 0.001$), and temporal resolution ($P < 0.05$). In one patient (SB) there was a significant improvement in the variability of temporal resolution ($P < 0.05$). In the two normal subjects, 75% of values showed a worsening of performance after 4-AP.

TABLE 3

RESULTS FOR GROUP 1 PATIENTS (HISTORY OF ON)

Mean of differences between paired values for placebo and 4-AP is shown with SEM and number of paired values in parentheses.

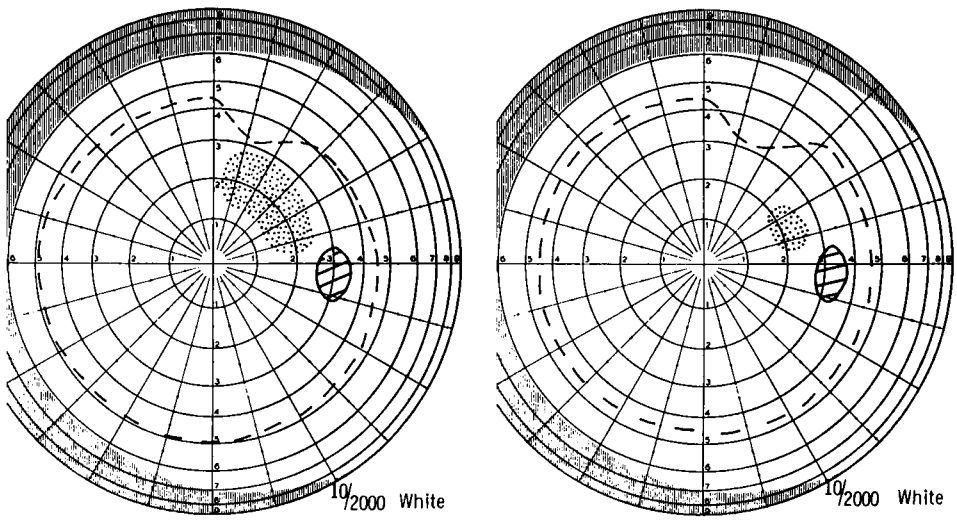
Patient	Luminance threshold (log cd.m^{-2})	Luminance threshold variability (log cd.m^{-2})	Temporal resolution (ms)	Temporal resolution variability (ms)
SB	0.016 (0.032, 6)	−0.051 (0.039, 6)	−1.54[a] (29.95, 5)	83.83[a] (38.17, 5)
LH	−0.185 (0.187, 3)	−0.036 (0.048, 3)	37.48 (33.37, 3)	30.88 (65.16, 3)
SC	0.071[b] (0.063, 3)	0.088[b] (0.043, 3)	32.51[b] (19.28, 3)	−8.96[b] (9.15, 3)
DW	0.751[c]	0.168[c]	33.91[c]	−10.48[c]
SH	0.126 (0.041, 6)	0.088 (0.016, 6)	4.91 (1.84, 6)	5.36 (3.28, 6)

[a] Measurements with placebo obtainable at 5 intervals, measurements with 4-AP at all 6 intervals.

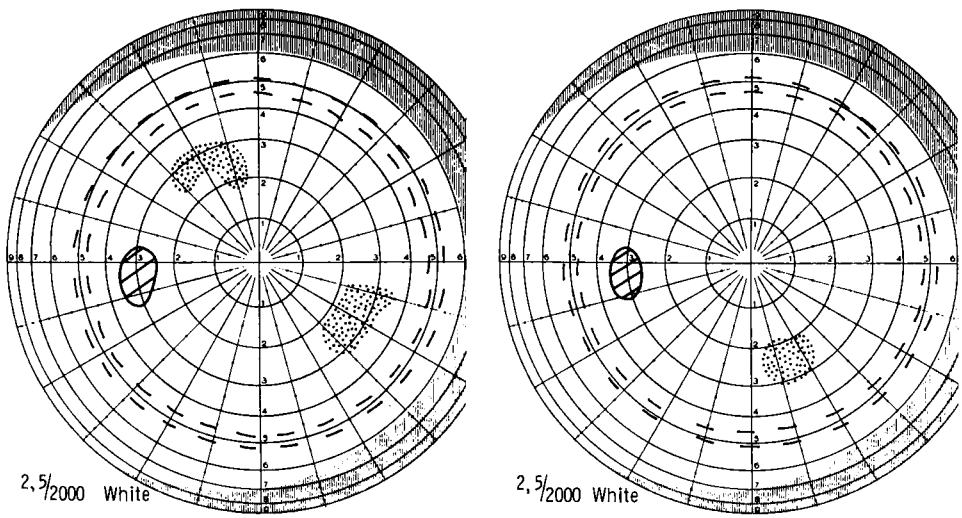
[b] No normalization of data with respect to baseline measurements since latter abnormal with respect to other estimates.

[c] Measurements with placebo obtainable at only 1 interval, measurements with 4-AP obtainable at all 6 intervals.

In the two patients with arcuate scotomata, the size of the scotomata was monitored during the course of the experiment. Administration of placebo had no effect on the size of the scotomata. In patient DW, following the administration of 4-AP there was a reduction in size of a scotoma (Figs. 1 and 2) and an improvement in visual acuity from N5 to N4.5. In patient SC, a scotoma disappeared following administration of 4-AP (Figs. 3 and 4). When perimetry was repeated the following day the scotomata had returned to their former size. In these two patients, the trend was for improvement in all the other visual parameters measured, except for variability in temporal resolution.



Figs. 1 and 2. Right visual field for patient DW before (left) and after (right) administration of 4-AP.



Figs. 3 and 4. Left visual field for patient SC before (left) and after (right) administration of 4-AP.

The effect of 4-AP on VEPs was studied in 2 patients: SH who had shown an improvement in all the previous visual measurements, and DW who had shown regression in the size of a scotoma following treatment. In patient SH, the latencies of the major positive and negative components in the right eye were effectively identical before and after administration of 4-AP, there being only a few ms difference between the two sets of readings. In patient DW, no consistent response could be recorded following the period of treatment. No conclusion can be drawn concerning the effect of 4-AP on VEPs in these two patients.

Group 2

Results obtained from patients in Group 2 (spinal MS) are illustrated in Table 4, following the same scheme as in Table 3. There was no change in the Kurtzke rating following either placebo or 4-AP. One patient noticed improvement in walking following 4-AP, and one noticed return in sacral sensation for the first time in 3 years, but this was not associated with any objective evidence of improvement. When the results of luminance threshold, its variability, temporal resolution and its variability were analysed for this group, 55% showed an improvement following administration of 4-AP, which was not significant ($P > 0.02$).

DISCUSSION

The results reported here do indicate that in certain selected patients with MS, treatment with 4-AP sigificantly improves transmission in demyelinated nerve pathways. The patients in Group 1 were chosen because of the presence of labile

TABLE 4

RESULTS FOR GROUP 2 PATIENTS (SPINAL MS)

Quantity shown is difference between paired values for placebo and 4-AP.

Patient	Luminance threshold (log cd.m^{-2})	Luminance threshold variability (log cd.m^{-2})	Temporal resolution (ms)	Temporal resolution variability (ms)
JL	−0.378	−0.534	—[a]	—[a]
JH	0.041	−0.040	−38.42	41.02
ML	0.043	−0.014	—[b]	—[b]
JB	0.019	−0.011	30.89	14.50
WW	−0.181	0.126	28.00	25.60

[a] Measurements with both placebo and 4-AP unobtainable.
[b] Measurements with 4-AP obtainable but not with placebo.

visual symptoms as it was felt that disorders in transmission might prove most readily reversible in this group. In patients in Group 2, with stable spinal MS, we were unable to demonstrate a significant overall effect following adminstration of 4-AP.

The basis for the improvement in transmission is probably related to alteration in the conduction safety factor. This is defined as the ratio of the action current of a nerve fibre to the minimum current necessary to maintain conduction (Tasaki 1953). It has been postulated that drugs that prolong the action potential duration should increase the conduction safety factor in demyelinated axons (Davis et al. 1970). Sherratt et al. (1980) have shown that in experimentally demyelinated rat nerve, 4-AP will prolong the action potential and overcome conduction block. Our results suggest that the drug has a similar effect in the human demyelinated optic nerve. It is not possible from our present data to make any inference about the relative contributions of 4-AP to improvement in trans-synaptic and axonal components of conduction.

Unfortunately, the toxicity of the drug limits its application. Although we did not encounter fits in any of our patients, grand mal seizures were observed by Ball et al. (1979) in 2 out of 4 patients treated with 4-AP for botulism. The most frequent side effects that we encountered were a subjective sensation of disorientation and painful dysaesthesia in the limbs. The development, therefore, of drugs that have an effect on the physiological process of conduction similar to that of 4-AP, but with less toxicity, is desirable for the symptomatic treatment of MS.

Because of the well-known variability of symptoms and signs in MS, assessment of the value of treatment has in the past been difficult and has relied largely on clinical evaluation which may give equivocal or unreliable results. The experimental approach described here takes account of some of these difficulties, and leads to a more objective means of assessing drugs in the treatment of the disease.

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