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4-Aminopyridine in Patients with Multiple Sclerosis: Dosage and Serum Level Related to Efficacy and Safety

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Summary: In a recent randomized, double-blind, placebo-controlled crossover trial, we demonstrated efficacy of 4-aminopyridine (4-AP) in improving disability of patients with multiple sclerosis (MS). Here we describe the relationship between dosage, serum level, efficacy, and safety of intravenously and orally administered 4-AP in the same group of 70 MS patients. After both intravenous and oral administration there was a significant relationship between serum levels and 4-AP doses used ($p < 0.001$ and $p < 0.01$, respectively). The use of 4-AP in oral doses three times a day showed a large variation and fluctuation in serum levels. After 12 weeks of oral treatment (maximum daily dosage 0.5 mg/kg body weight), a statistically significant improvement was found for the smooth pursuit gain of the eye movements (estimated effect 0.14, 95% confidence interval 0.06–0.23, $p < 0.001$). The amount of improvement was significantly related to 4-AP serum levels ($p = 0.0013$). Side effects after intravenous 4-AP occurred frequently and were very troublesome (pain in infusion arm, dizziness). Side effects during oral treatment (dizziness, paresthesias) were very mild and occurred 30–45 min after intake of the medication and could be related to high serum levels. **Key Words:** Multiple sclerosis—4-Aminopyridine—Eye movement registration.

In 1924 Dohrn (1) described the pharmacological properties of the aminopyridines and noted the excitatory effect of 4-aminopyridine (4-AP) on the central nervous system. Later research showed that aminopyridines block potassium channels in excitable membranes and facilitate chemical synaptic transmission at central, autonomic, and neuromuscular synapses (2–5). In several small studies beneficial effects of 4-AP have been demonstrated in disorders of neuromuscular transmission and in multiple sclerosis (MS) (6–12). Until now the clinical applications of the drug have been very limited, since significant side effects of 4-AP,

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such as a confusional state and epileptic fits, were reported in some of these studies (7,9). Pharmacokinetic data have been investigated in only one study which included seventeen MS patients (13).

Recently we performed a randomized, placebo-controlled, double-blind, cross-over study in 70 patients with MS to further investigate the effects of 4-AP (14). In this study, it was demonstrated that 4-AP may have a favorable effect on the disability of MS patients as measured by the Kurtzke expanded disability status scale (EDSS).

In this report we describe the relationship between dosage, serum level, efficacy, and safety of 4-AP in these patients. In the present analysis, the EDSS was not used to assess efficacy, because grading disability using this scale is rather subjective; this increases interobserver variability and inhibits detection of minor treatment-induced changes (15). In a previous study, we demonstrated that the registration of eye movements, especially of smooth pursuit gain, is a reliable and sensitive method in the assessment of neurological functions in MS patients (16). Therefore, we expected that this technique could also quantify effects of 4-AP in relation to dosage and serum levels. All patients were treated with intravenous 4-AP as well as oral 4-AP in order to compare both treatments.

SUBJECTS AND METHODS

Subjects

Seventy patients (43 women and 37 men) with clinically definite or laboratory-supported definite MS according to the Poser criteria entered the trial (17). Their ages ranged from 23 to 68 years (mean 41.6 years), duration of the disease ranged from 2 months to 25 years (mean 86 months) and the EDSS ranged from 2.0 to 7.5 (mean 5.0) (18). The patients had no hepatic or renal disease or a medical history of epileptic fits. Informed consent was obtained from all patients before being accepted into the study. The protocol was approved by the Ethical Committee of the Free University Hospital, Amsterdam.

Study Design

The study was divided into two phases. In phase I 4-AP was administered intravenously and in Phase II 4-AP was administered orally. Both phases had a randomized, double-blind, placebo-controlled, cross-over design. In phase I every patient underwent two sessions separated by a 1 week interval, one with 4-AP and one with placebo (NaCl 0.9%) administered intravenously in a randomized sequence. Patients received the drugs in doses of 1 mg in 1–2 minutes every 20 min during the first hour and in doses up to 2.5 mg in 1–2 minutes every 20 min afterwards. The infusion was terminated when troublesome side effects occurred or a maximum dose of 0.5 mg/kg body weight was given.

One week after the intravenous treatment the patients entered phase II. In this phase, nonenteric-coated capsules containing 4-AP or placebo (avicel) were administered orally for a period of 12 weeks each in a randomized sequence. The starting dosage was 10–20 mg orally per day in 2–3 divided doses. The daily

dosage was elevated with 5–15 mg at week 2 and 6, or week 14 and 18. The ultimate dosages were determined on the basis of occurring effects or side effects up to a maximum of 0.5 mg/kg body weight each day.

Efficacy and Safety Parameters

Efficacy was assessed by registering horizontal smooth pursuit eye movements. Patients were seated and viewed a horizontal semicircular lightbar stimulator from a distance of 2 m. Eye position was recorded by an infrared scleral reflection technique. Horizontal smooth pursuit eye movements were stimulated by a sinusoidal moving target at frequencies of 0.1, 0.2, . . . , 0.7 Hz, with an amplitude from −20 to +20°.

During the pursuit registrations the target velocity was increased until the smooth pursuit movements were replaced by saccades. The quantitatively determined parameter was the smooth pursuit gain (eye velocity/target velocity). The gain was derived from the recording of three sessions each for 1 min with a 1-min rest period between each session (16). During phase I, electrocardiography (ECG) was performed before and immediately after the administration of 4-AP and placebo. During phase II electroencephalograms (EEGs) were recorded on a 16-channel Siemens Elema Machine using the international 10–20 system of electrode placement with referential source and bipolar montages (bandwith 3 dB; 0.26–30 Hz). Hyperventilation and photic stimulation were done routinely during recording of at least 20 min. The EEGs were recorded before the start of phase II and after 2 weeks of each oral period. The EEGs were scored by conventional visual inspection by an experienced neurophysiologist who was aware of the study protocol but unaware of the clinical history of the patient and the medication used.

The appearance or increase during the study of generalized or focal slow wave activity and the generation of spikes, sharp waves, or spike-waves that could clearly be distinguished from background activity were considered to be significant changes in the EEG. If compared with the baseline EEG, no significant changes were found in both EEGs recorded during the oral treatment, the neurophysiologist was asked to make a forced choice between these two recordings, indicating which EEG was most disturbed on account of minor changes (excess of fast activity, slight focal abnormalities).

During phase II, blood examinations (hemoglobin, white cell count, platelets, urea, creatinine, total protein, alkaline phosphatase, aspartate and alanine aminotransferases, γ-glutamyl transpeptidase, sodium, potassium) were performed before entry into the study and at weeks 2, 12, 14, and 24.

During both treatment phases, all subjective side effects or concomitant diseases that were mentioned by the patients were registered.

4-AP Serum Levels

In phase I, blood samples were obtained from the noninfusion arm to determine 4-AP serum levels immediately after the termination of drug administration. In 16 patients (8 women and 8 men), selected because they were highly cooperative, blood samples were obtained repeatedly at defined intervals during both treatment

sessions of phase I (T1: 60–100 min after starting the infusion; T2: directly after ending the infusion; T3: 90–180 min after ending the infusion. The ages of these patients ranged from 24 to 57 years (mean 42.9 years), duration of disease ranged from 21 months to 12.2 years (mean 10.2 years) and EDSS ranged from 4.0 to 7.5 (mean 5.9). At the same time that the blood samples were obtained, registration of smooth pursuit eye movements was performed.

In phase II, blood samples were obtained to determine 4-AP serum levels at the end of the first and second oral treatment periods 1.5–2.5 h after the last intake of medication (weeks 12 and 24).

After breaking the code, in one patient (female, 57 years) who at that moment was treated in an open label fashion with oral 4-AP in a dose of 10 mg three times a day, blood samples were taken at frequent intervals in order to measure 4-AP serum levels throughout the day (every 15 min during the first hour after each 4-AP intake, every 30 min in the second hour after each intake, and finally, 3 hours after each intake). Serum levels of 4-AP were determined by high-performance liquid chromatography (HPLC) with solid phase extraction (19).

Data Analysis

To study the dependency of 4-AP serum levels on the total given dosage and the dependency of the increase in smooth pursuit gain on 4-AP serum levels, linear regression methods were used. To test the significance of averages over time the one-sample t test was used. A p value of <0.05 was considered significant. A detailed description of the analysis of efficacy and side effects in the cross-over design has been described elsewhere (14). Both during the intravenous and the oral treatment phase, the estimated effect of 4-AP was determined by subtracting the response during the first treatment period from that observed during the second treatment period. As demonstrated in a previous study, in individual patients a change in the smooth pursuit gain of 0.09 was considered significant (16).

RESULTS

Intravenous Phase

The administered dosages of 4-AP in this phase ranged from 4.5 to 30.5 mg (0.07–0.5 mg/kg body weight). The infusion duration ranged from 60 to 260 min. The 4-AP serum levels ranged from 24 to 114 ng/ml (mean 61.8 ng/ml). On average, the 4-AP serum levels increased 3.8 ng/ml per mg 4-AP per day ($p < 0.001$).

Smooth pursuit gain improved statistically significantly after infusion of 4-AP (estimated effect 0.10, 95% confidence interval 0.07–0.13, $p < 0.0001$). Side effects that were reported during infusion of 4-AP are listed in Table 1. In 32 patients these side effects were considered reason to stop the infusion. Pain or paresthesias in the infusion arm were most often reported as side effects. These symptoms were reported after infusion of 1–2.5 mg 4-AP and could not be avoided or reduced by rapidly flushing the needle with 0.9% NaCl directly after the infusion. Dizziness and light-headedness were experienced as serious and troublesome in 25 patients. These effects always occurred at higher doses than the local side effects.

TABLE 1. *Minimal dose at which side effects occurred during intravenously administered 4-aminopyridine*

Side effects	Number of patients	Minimal dose (mg)
Paresthesias in infusion arm	49	1
Perioral paresthesias	6	1
Dizziness/light-headedness	19	9
Dizziness/light-headedness and nausea/vomiting	2	10
Dizziness/light-headedness and a feeling of restlessness	4	9
Headache	1	20

All side effects gradually reversed within 2 hours after discontinuing the infusion. Seven patients did not encounter any side effects during infusion.

There were no differences between the ECG registrations that were performed directly before and after intravenous administration of the drug. Figure 1 shows the relationship between 4-AP serum levels and treatment-induced changes as measured with the horizontal smooth pursuit eye movements in the subgroup of 16 patients. At time T1 (mean 80 min after starting infusion) the dose of 4-AP was 6.7 mg (range 5–9 mg). At this point the mean serum level of 4-AP was 38.1 ng/ml (range 24–55 ng/ml).

Directly after ending the infusion of 4-AP (T2), the mean serum level was 62.4 ng/ml (range 26–86 ng/ml) after a mean total dosage of 15.5 mg (range 9–20 mg). At time T3 (mean 120 min after the end of infusion) the mean serum level of 4-AP was

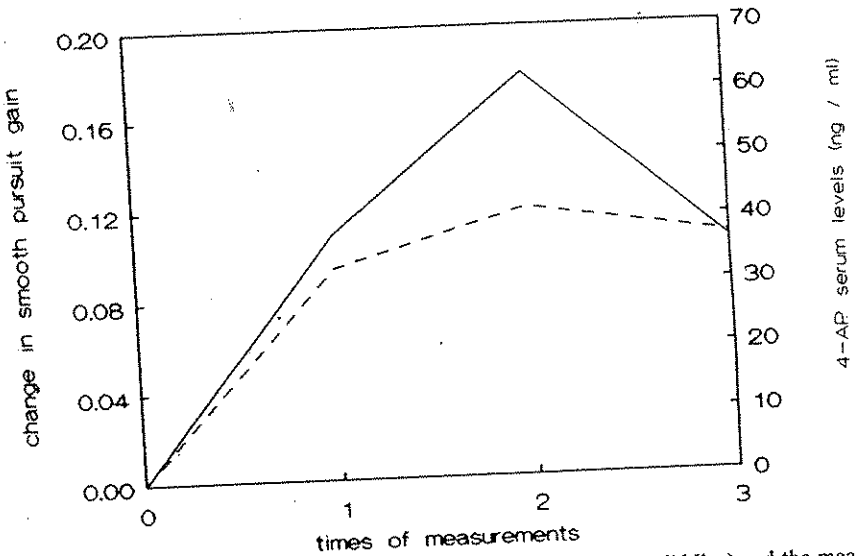

FIG. 1. Relationship between the mean change in smooth pursuit gain (solid line) and the mean 4-AP serum level (dotted line) measured at fixed time points in 16 patients during 4-AP infusion. Times of measurement: 0, before infusion; 1 (T1), mean 80 min after starting infusion; 2 (T2), directly after ending infusion; 3 (T3), mean 120 min after ending infusion. For details see text.

36.3 ng/ml (range 22–58 ng/ml). An increase of the smooth pursuit gain was found at T1 (mean increase in gain +0.094, $p < 0.01$) and at T2 (mean increase in gain compared with T1 +0.025, $p = 0.25$). At time T3 there was a slight decrease in the smooth pursuit gain compared with T2 (mean decrease 0.013, $p = 0.58$). Whereas 4-AP serum levels decreased rapidly after ending the infusion, the degree of improvement in smooth pursuit eye movement decreased to a lesser extent.

Oral Treatment

Sixty-nine patients entered the oral treatment phase (one patient did not start this phase because of reasons not related to the study). The mean dosage of 4-AP that was administered during this phase was 31.2 mg/day (range 10–50 mg/day), divided in 2–4 doses.

The 4-AP dose/kg body weight ranged from 0.17 to 0.55 mg. In the 4-AP treatment period serum levels ranged from 7 to 107 ng/ml (mean 53.6 ng/ml). On average, 4-AP serum levels increased 1.3 ng/ml per mg 4-AP per day ($p < 0.01$).

A statistically significant effect of 4-AP was found for the smooth pursuit gain (estimated effect of 4-AP 0.14, 95% confidence interval 0.06–0.23, $p < 0.001$). The amount of improvement of the horizontal smooth pursuit gain was significantly related with 4-AP serum levels ($p = 0.0013$). The smooth pursuit gain increased 0.002 per ng/ml 4-AP. The serum level of 4-AP above which the smooth pursuit gain improved, fluctuated between patients. In one patient, a significant improvement of smooth pursuit gain occurred at a 4-AP serum level of 33 ng/ml. In another patient, no improvement was detected at a 4-AP serum level of 40 ng/ml, whereas in the first patient a 4-AP serum level of 75 ng/ml corresponded to a significant improvement of the smooth pursuit gain.

In individual patients, the presence or absence of a significant improvement in smooth pursuit gain was related to the 4-AP serum level. In this analysis, an arbitrarily chosen level of 60 ng/ml was used as cut-off point. Thirty-seven percent of the patients showed a significant improvement of the smooth pursuit gain; 53% of these patients had a 4-AP serum level above 60 ng/ml. Sixty-three percent of the patients showed no improvement of the smooth pursuit gain; 19% of these patients had a 4-AP serum level above 60 ng/ml.

Side effects reported during phase II are summarized in Table 2. These side

TABLE 2. *Minimal daily dose at which side effects occurred during orally administred 4-aminopyridine*

Side effects	Number of patients	Minimal daily dose (mg)
Paresthesias/dysesthesias (perioral, acral)	15	5
Dizziness/light-headedness	36	5
Gait instability	11	5
Nausea/vomiting	9	5
Restlessness/anxiety	4	5
Abdominal pain	5	10
Obstipation	1	25

effects were reported at a daily dosage ranging from 5 to 50 mg occurring after single doses of 5–20 mg 4-AP. In general these side effects were reported to be mild. Dizziness and light-headedness were less serious when compared with the effects after intravenous 4-AP administration. However, 14 patients needed dose reduction and three patients withdrew from the study because of these side effects. Most patients reported side effects 30–45 min after taking the medication; these effects generally resolved within 2 to 5 h. Fifteen patients did not experience side effects. In these, the total daily dose of 4-AP ranged from 25 to 30 mg (0.38–0.55 mg/kg body weight) with serum levels ranging from 7 to 106 ng/ml. In two patients significant changes were found in the EEG registration. In one patient generalized spikes and spike-waves were recorded during oral 4-AP administration and in one patient a significant increase in temporal slow-wave activity was observed during placebo administration.

A forced choice between EEGs recorded during 4-AP and placebo could be made in 19 patients. Minor EEG changes were found in 13 patients during 4-AP and in 6 patients during placebo treatment ($p = 0.17$). EEG changes were not related to the dosage of 4-AP used.

The blood tests performed after treatment with 4-AP and placebo did not show any significant effects of 4-AP (all data $p > 0.05$).

During this treatment phase, a number of incidental illnesses were reported. Diagnoses were cystitis (2 patients), stomatitis (1 patient), transient urticaria (1 patient), fracture of a metacarpal bone (1 patient), and a severe distortion of the ankle (1 patient) during administration of 4-AP and cystitis (1 patient), angina of the throat (1 patient), deep venous leg thrombosis (1 patient), and a fracture of the collum of the hip (1 patient) during placebo treatment. The illnesses occurring during 4-AP treatment were neither related to the dosage nor to the time since starting treatment. Figure 2 shows serum levels of 4-AP in the individual patient who received 10 mg 4-AP three times a day (range 18–118 ng/ml) with a peak serum level 30 min after intake of the first dose. It might be relevant that the first dose of 4-AP was given with only a very slight breakfast whereas both subsequent doses were combined with larger meals.

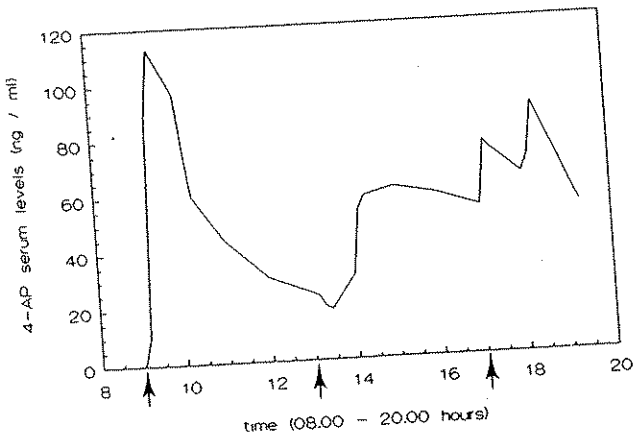

FIG. 2. Daily curve of serum levels in a patient using oral 4-AP in a dose of 10 mg, three times a day. The arrows indicate the times of intake. For details see text.

DISCUSSION

During the first clinical experience with 4-AP, the drug was used to antagonize the effects of the nondepolarizing neuromuscular blocking agents in anesthesiology (20). Since then, 4-AP has been used clinically in patients with Lambert–Eaton syndrome (6,9), myasthenia gravis (8,9), human botulism (7), Huntington's disease (21) and Alzheimer's disease (22). A number of recent studies pointed to the potential efficacy of 4-AP in the treatment of MS (10–14). The favorable effects in MS were explained by the potassium channel-blocking effects of 4-AP which restore nerve conduction in demyelinated nerve fibers by prolongation of the repolarization phase of the action potential.

The present study, including 70 MS patients who were treated with 4-AP for a maximum period of 12 weeks, shows that serum levels reflect doses of both intravenously and orally administered 4-AP. Assessment of 4-AP serum levels throughout the day in one patient showed large fluctuations. Uges et al. studied three patients and found that orally administered 4-AP (10 mg t.i.d.) resulted in serum peak levels of 75–150 ng/ml 1–3 hours after intake (23). Our individual female patients shows comparable values when taking 4-AP at 13.00 and 17.00 h. However, taking 4-AP at 9.00 h after only a light meal leads to an early and high serum peak level. These results suggest that the intake of food may partly be of influence on serum peak fluctuations.

The results of our study show that smooth pursuit gain improves both after intravenously and orally administered 4-AP. These findings confirm our clinical data on the efficacy of 4-AP in improving signs and symptoms of MS (14). During oral treatment with 4-AP the magnitude of improvement, as defined by the increase in smooth pursuit gain was significantly related to the 4-AP serum level. In the intravenous phase we also found a clear relationship between smooth pursuit gain and 4-AP serum levels in the subgroup of patients who were studied serially. In contrast Stefoski et al. (13) did not find this relationship. These authors found that improvements of videotaped neurologic examination, vision (critical flicker fusion), and visual evoked potential were not correlated with either dosage or serum level of 4-AP. An explanation for this difference could be the higher sensitivity of eye movement registration in the assessment of treatment effects. This is in accordance with our previous findings that sensitivity of eye movement registration is higher than the sensitivity of the visual evoked potential in the evaluation of therapy in patients with MS (16).

Side effects of 4-AP seem to be predominantly associated with the function of the central nervous system. Restlessness, confusion, and generalized tonic-clonic seizures have been reported at doses higher than 0.8 mg/kg body weight (7,9). The absence of epileptic fits and significant changes in the EEG during 4-AP in our study may be explained by our dosage scheme which allowed a maximum daily dose of only 0.5 mg/kg body weight. Minor side effects like dizziness and paresthesias were frequently encountered in both the intravenous and oral treatment phase. These side effects occurred at highly variable doses. The side effects in the intravenously treated patients occurred frequently and were very troublesome. Therefore, we cannot recommend administration of 4-AP intravenously. In the

orally treated patients, side effects were mild and always reached a maximum 30 to 45 minutes after intake of 4-AP. This might be an indication that at the moment of side effects, serum peak levels of 4-AP are reached. This is supported by our findings in individual patients showing a serum peak level 30 min after the intake of the first dose of 4-AP. These results confirm the finding of Uges et al. (23) that subjective side effects were an indication of a high serum level of 4-AP.

Until now there has been but little information on the effects of 4-AP on bone marrow, renal, cardiac, or hepatic function in humans. Our results, showing no abnormalities in laboratory tests or ECGs, demonstrate that 4-AP can be used safely in doses up to 0.5 mg/kg body weight.

Based upon the observations in our study, it may be concluded that higher dosages and serum levels are likely to produce greater improvement in those MS patients who are capable of favorably responding to 4-AP. With a maximal daily dosage of 0.5 mg/kg body weight no serious side effects were registered. The use of 4-AP in oral doses three times a day gives rise to a large variation and fluctuation in serum levels with high peaks related to subjective side effects. These findings suggest that better control of 4-AP serum levels, for example, by using a slow-release preparation, may have a favorable impact on the ratio between efficacy and safety in the treatment of patients with MS.

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