
To Print: Click your browser's PRINT button.

NOTE: To view the article with Web enhancements, go to:

<http://www.medscape.com/viewarticle/458857>

Efficacy and Safety of 4-Aminopyridine in Patients With Long-Term Spinal Cord Injury:
A Randomized, Double-Blind, Placebo-Controlled Trial

Israel Grijalva, M.D., Ph.D., Gabriel Guízar-Sahagún, M.D., Ph.D., Gilberto Castañeda-Hernández, Ph.D., Dolores Mino, M.D., M.S., Héctor Maldonado-Julián, M.D., Guadalupe Vidal-Cantú, M.S., Antonio Ibarra, Ph.D., Omar Serra, M.D., Hermelinda Salgado-Ceballos, Ph.D., and Rita Arenas-Hernández, M.S.

Pharmacotherapy 23(7):823-834, 2003. © 2003 Pharmacotherapy Publications

Posted 07/25/2003

Abstract and Introduction

Abstract

Objectives: To study the efficacy and safety of 4-aminopyridine (4-AP), and to document sensorimotor changes after discontinuation of the drug in patients with long-term spinal cord injury.

Design: Randomized, double-blind, placebo-controlled trial.

Setting: Clinical research unit.

Patients: Twenty-seven patients with long-term spinal cord injury.

Intervention: Patients were randomized to receive either oral 4-AP 5 mg/day, which was increased by 5 mg/week to a maximum dosage of 30 mg/day, or placebo for 12 weeks. They switched to the opposite treatment for the next 12 weeks.

Measurements and Main Results: Twenty-five patients finished the study. The results from the first 12 weeks were used to test efficacy. Positive gains in motor function, sensation, and independence occurred more frequently in patients receiving 4-AP (69%) than those receiving placebo (46%). Significant functional improvement was also noted in those treated with 4-AP (χ^2 , $p=0.042$). When each evaluation scale was considered

separately, significant improvement was seen only in motor function (4-AP 92% vs placebo 46%, Fisher exact test, $p=0.03$). Persistent effects of the drug were assessed at week 24 in the group that initially received 4-AP. A persistent, significant 4-AP effect was observed in evaluations of sensation and independence (67% and 83% of patients, respectively; Wilcoxon signed rank test, $p=0.032$ and 0.042 , respectively). Fourteen (56%) patients had 26 adverse reactions. One moderate adverse reaction - posterior tibial artery vasospasm - and 25 mild adverse reactions, such as dry mouth, dizziness, nausea, gastritis, oral and peripheral paresthesia, resolved adequately. Six (24%) patients experienced transitory alterations of enzyme levels (alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, and creatine kinase) and thrombocytopenia.

Conclusion: Patients who received 4-AP showed significant improvement in motor function, and a persistent effect on sensation and independent function occurred. The drug is safe; however, after starting 4-AP therapy, patients must be carefully monitored for the possible occurrence of peripheral vasospasm.

Introduction

Spinal cord injury (SCI) in humans leads to motor, sensory, and autonomic dysfunction. No therapeutic strategy has been unquestionably accepted that significantly improves neurologic alterations in the acute^[1, 2] or chronic stage.^[3, 4] After SCI, many of the axons that survive in the epicenter of the injured zone are demyelinated.^[5-7] Since demyelination may be an important contributing factor to long-term sensory and motor impairment,^[8, 9] restoration of conduction in demyelinated fibers has been identified as an important strategy for promoting functional recovery.^[9-15] Postmortem examination of humans with SCI indicates that almost two thirds have partially spared spinal cord. In about half of the patients with functionally complete injury, nerve fibers traversed the lesion site.^[16] The loss of functionality can be partially due to demyelination of the preserved axons, as SCI animal models have shown.^[9-15, 17]

4-Aminopyridine (4-AP) blocks voltage-gated, fast potassium channels. The drug may be capable of improving neurologic function by restoring conduction in demyelinated axons,^[8-15] enhancing synaptic efficacy,^[15] potentiating transmitter release at the neuromuscular junction level,^[18] and increasing skeletal muscle twitch tension.^[19] Several SCI animal models have shown that 4-AP produces significant improvement in both behavioral and electrophysiologic evaluations.^[9-11, 13-15, 20] Experimental studies of 4-AP in humans with SCI have demonstrated improvement in several functions.^[3, 21-28]

Single intravenous or long-term oral 4-AP administration induces a persistent neurologic gain of 24-48 hours^[21, 22] to 1-2 weeks^[26, 27] in some patients. However, interpretation of most clinical results of 4-AP therapy in patients with SCI is limited by the fact that the data were obtained in open trials. Interpretation is further complicated by the fact that the results of the two blinded, randomized, crossover, behavioral clinical trials reported in the literature yielded contradictory results.^[3, 4]

Concerning safety in patients with SCI, several adverse reactions occurred in those who

received oral 4-AP 10-45 mg/day during treatment periods of 2 weeks-4 months. Adverse reactions included lightheadedness, nervousness, dizziness, gastric upset, nausea, and abdominal cramps.^[3, 4, 26, 27] Characteristics and time dependency of these adverse reactions, however, have not been described in detail.

Our objective was to study the efficacy and safety of 4-AP, and to document sensorimotor changes after discontinuation of the drug in patients with long-term SCI.

Methods

This study was conducted from September 1999-June 2000 at the Spinal Cord Clinic of the Research Medical Unit for Neurological Diseases at the Specialties Hospital, Centro Médico Nacional Siglo XXI, of the Instituto Mexicano del Seguro Social (IMSS) in Mexico City. The study was initiated after its acceptance by both the local research committee of the hospital and the National Research Council of the IMSS. All patients were fully informed about the trial, all received a written description of the trial, and their questions and concerns were answered orally. All patients signed an informed consent letter. The Spinal Cord Clinic is a referral center of institutional practice mainly of ambulatory care.

A randomized, double-blind, placebo-controlled trial comparing 4-AP with placebo was conducted; details of the design are shown in Figure 1. Identical capsules containing 4-AP 5 mg or placebo were prepared. The 4-AP was given as gelatin capsules containing 4-AP 5 mg and microcrystalline cellulose as the excipient. Placebo capsules contained only the excipient. Each patient was administered two capsules every 8 hours, for a total of six capsules/day. Initially, all patients completed a run-in period of 2 weeks with placebo. Patients randomized to the 4-AP-placebo sequence then received one 4-AP capsule and five placebo capsules/day for 1 week (i.e., 4-AP dosage was 5 mg/day). The 4-AP dosage was increased by 5 mg/week by substitution of placebo by 4-AP capsules, such that patients received six capsules/day throughout the study. At 6 weeks, patients in the 4-AP group were receiving 4-AP 30 mg/day. The 30-mg/day dosage was maintained for 7 weeks. These patients then switched to the opposite treatment and received placebo (six capsules/day) for 12 weeks.

Patients in the placebo-4-AP sequence received placebo for 12 weeks after the run-in period. Then they received 4-AP starting with 5 mg/day, increasing by 5 mg/week to a maximum of 30 mg/day, and maintaining the 30-mg/day dosage for 7 weeks, as described above. There was no washout period. The strategy of giving six capsules/day allowed us to increase the 4-AP dosage gradually while maintaining the double-blind study design.

Patient Selection

Patients with SCI were eligible for the study if they met the following criteria: tetraplegia or paraplegia for more than 1.5 years before the study began, aged 18-60 years, neurologic injury level of C4-L1, medically stable and able to breathe independently,

stable neurologic deficits for more than 90 days before the study, absence of epileptic antecedent and electroencephalogram without epileptic activity, and paralyzed extremities without passive limitations (healthy joints). In addition, women had to be postmenopausal or surgically sterile, or using an acceptable method of birth control.

Exclusion criteria were the following: pressure ulcers, skin infections, or phlebitis; history of cardiovascular disease (syncope, arrhythmia, or myocardial infarction within the last 2 years); systolic blood pressure greater than 150 or less than 70 mm Hg, diastolic blood pressure greater than 110 or less than 50 mm Hg, or heart rate greater than 110 or less than 50 beats/minute; impaired hepatic function (total hepatic enzyme or bilirubin levels greater than 2 times the upper limit of normal) or impaired renal function (creatinine level greater than 2 times the upper limit of normal) less than 6 months before the study; known allergy to pyridine-containing drugs; neurologic, degenerative, or psychiatric disorders that would impair the patient's ability to complete the protocol; any illness or abnormality that would jeopardize patient safety or interfere with the conduct of the study; history of substance abuse; and inability to discontinue excluded concomitant drug therapy.

Patients also were excluded if they were receiving treatment with an antispasticity compound and could not maintain a stable daily dosage, were pregnant or lactating, had received any other investigational drug less than 30 days before the study, or had received any drug known to cause significant major organ toxicity less than 3 months before the study. Patients were removed from the study if they experienced moderate-to-severe adverse reactions or had bilirubin and enzyme levels greater than 2 times the upper limit of the normal range, or if alterations in other laboratory values were associated with mild adverse reactions. Patients were also eliminated if they became pregnant or voluntarily dropped out.

Clinical Evaluation

Clinical evaluation was performed with the American Spinal Cord Injury Association (ASIA) motor function and sensory scale^[29] and the Spinal Cord Independence Measure.^[30] Within 2-4 weeks after the study began, all patients underwent pretreatment evaluation. Additional evaluations were performed at 12 and 24 weeks of the follow-up. All evaluations were performed by the same clinical investigator.

Sensory function was tested and scored for two modalities, pin prick and light touch, in all dermatomes; muscle strength was tested in each of the 20 key muscles.^[29] Evaluation of both sides was expressed in a single score. The ASIA Impaired Scale (AIS)^[29] was used to classify the injuries as complete or incomplete. Patients with AIS grades A and B injuries, with spared motor voluntary movements caudal to the neurologic injury level (zone of partial preservation), received AIS grades A+ and B+.

The Spinal Cord Independence Measure was used to evaluate independence.^[30] This scale has 16 questions on self-care, respiratory and sphincter management, and mobility in and out of home. The scale ranges in points from 0 (total dependence) to 100 (total

independence).

Safety Evaluation

Safety surveillance was done every 4 weeks from the beginning of the study, with a search for adverse reactions, assessment of vital signs, and performance of physical examinations and laboratory tests. Blood and urine samples were obtained during each patient visit to determine concentrations for glucose; creatinine; blood urea nitrogen; total cholesterol; triglycerides; total, direct, and indirect bilirubin; alanine aminotransferase (ALT); aspartate aminotransferase (AST); alkaline phosphatase (ALP); creatine kinase (CK); lactic acid dehydrogenase; sodium; potassium; chloride; calcium; and phosphorus. A complete blood cell count with differentials and a routine urinalysis and urine culture were also obtained at each visit.

Each suspicious symptom of an adverse reaction was evaluated according to a published protocol.^[31] An adverse reaction was defined as an appreciable harmful or unpleasant reaction experienced by a patient as a result of the drug therapy. All adverse reactions causally or not associated with the drug administered were documented from the start and followed until resolution. Adverse reactions were classified as fatal (death), severe (life threatening), moderate (not life threatening but requiring hospitalization, emergency attention, or absence from work or school), or mild (all others).

Efficacy and Safety Criteria

The results after 12 weeks of treatment with 4-AP or placebo were used to assess efficacy. Pretreatment and final (during the 12th week of treatment) scores of the ASIA motor function and sensory scale and the Spinal Cord Independence Measure were obtained. Efficacy was established if significant favorable changes occurred in the 4-AP group. Any possible gain was considered success; further impairment or absence of change was considered failure.

For safety, the 26 weeks of the study were assessed (included the 2-week run-in placebo period). A persistent 4-AP effect was considered established if after 12 weeks of drug discontinuation the final scores were significantly higher than pretreatment scores. Percentage of change was determined according to functional recovery rate^[32] by using the following formula: $(\text{final score} - \text{pretreatment score}) / (\text{total score} - \text{pretreatment score})$.

Randomization and Blinding

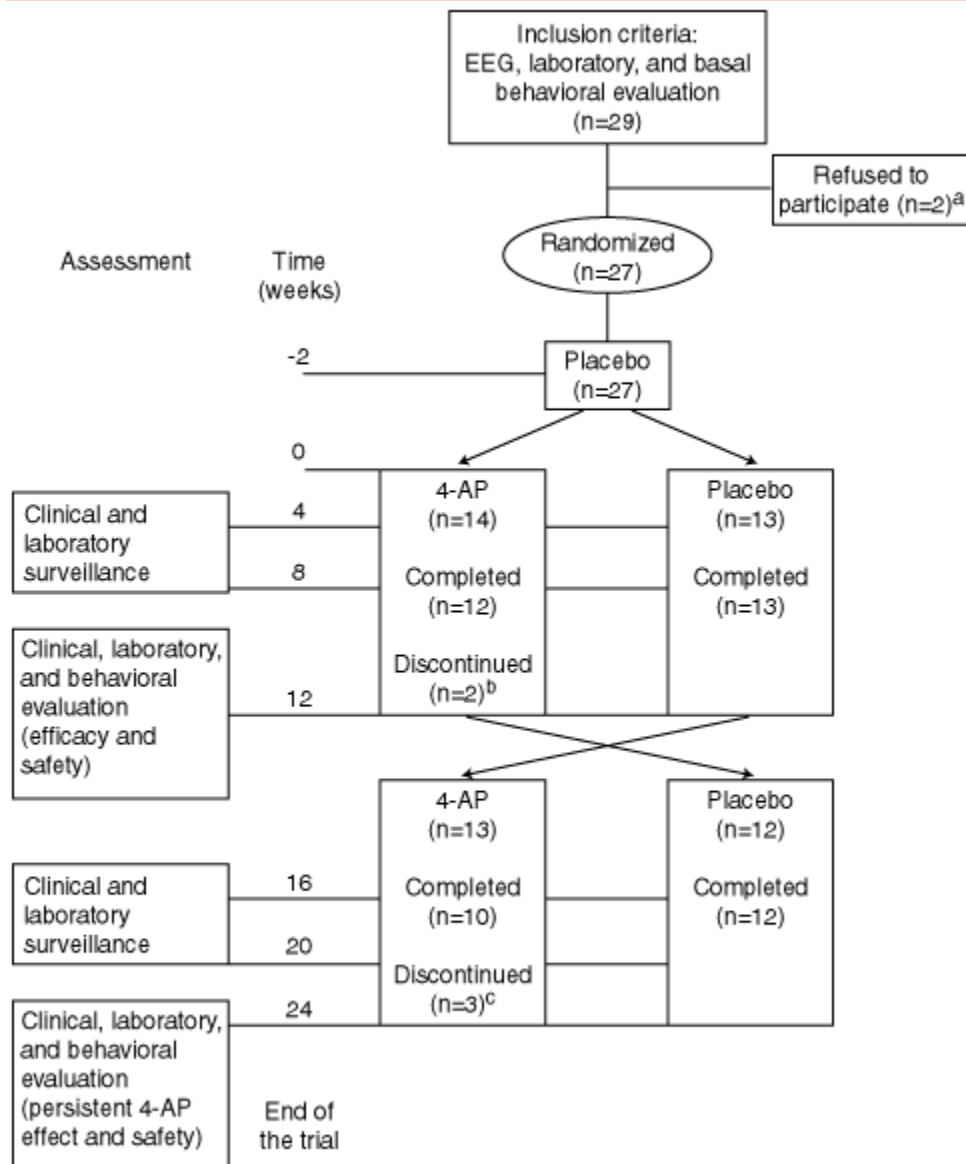
A progressive number was assigned to each patient who satisfied the selection criteria during the recruitment period. The patient's initials and consecutive numbers were submitted to the pharmacologic group who assigned patients to groups of five for randomization. The research team did not know which patients received active drug or placebo.

Statistical Analyses

To test efficacy, successes and failures in each group were evaluated by the χ^2 or Fisher exact tests. To test 4-AP persistent effects, pretreatment and final scores were evaluated by the Wilcoxon signed rank test. All statistical tests were done with GraphPad Prism software, version 3.0 (GraphPad Prism, Inc., San Diego, CA). For all comparisons, a p value of less than 0.05 (two-tailed) was considered significant. Descriptive statistics were used for these and other outcomes, and the results were expressed as mean \pm SD, percentage, or total number of cases (for safety).

Results

The flow diagram in Figure 1 illustrates patients included and excluded, and timing of assessment.



Source: Pharmacotherapy © 2003 Pharmacotherapy Publications

Figure 1. Design of the clinical trial.

^aOne patient left the country to undergo special intensive physical therapy, and one lived out of the city and could not come in often enough for surveillance.

^bOne patient was out of town due to a family situation, and one incurred a urethral injury during cystoscopy and underwent suprapubic cystostomy.

^cOne patient was excluded due to a moderate adverse reaction. One who took higher doses of 4-AP experienced hypotonia of the lower limbs, which impeded ambulation for 1 day; the patient then dropped out of the study. One patient did not attend the last evaluation. All three patients took 4-AP for enough time to be included in the safety evaluation.

Patient Data

Twenty-seven patients started the study; 25 (21 men, 4 women) completed it. Mean age

at the start of the study was 33.4 ± 8 years (range 23-48 yrs); time since SCI was 7.1 ± 3.2 years (range 1.5-15 yrs). Injury level, type of injury, and AIS grade are shown in [Table 1](#). Behavioral pretreatment scores comparing 4-AP and placebo groups did not show significant statistical differences.

Efficacy

Motor function, sensation, or independence measures changed in patients receiving 4-AP 15 mg/day or higher. In some patients, success required a dosage of 4-AP 30 mg/day for more than 1 week. One of two patients receiving 30 mg/day required that dosage for more than 1 week to experience improvement; the other required it for 4 weeks. Efficacy in all three areas was achieved in the first treatment period of the study. The success rate was 69% for the 4-AP group (25/36 areas) versus only 46% (18/39) for the placebo group; the difference was significant (χ^2 , $p=0.042$; Figure 2). When each scale was considered separately, improved motor function was seen in 11 of 12 patients receiving 4-AP and in 6 of 13 receiving placebo (Fisher exact test, $p=0.03$; Figure 2).

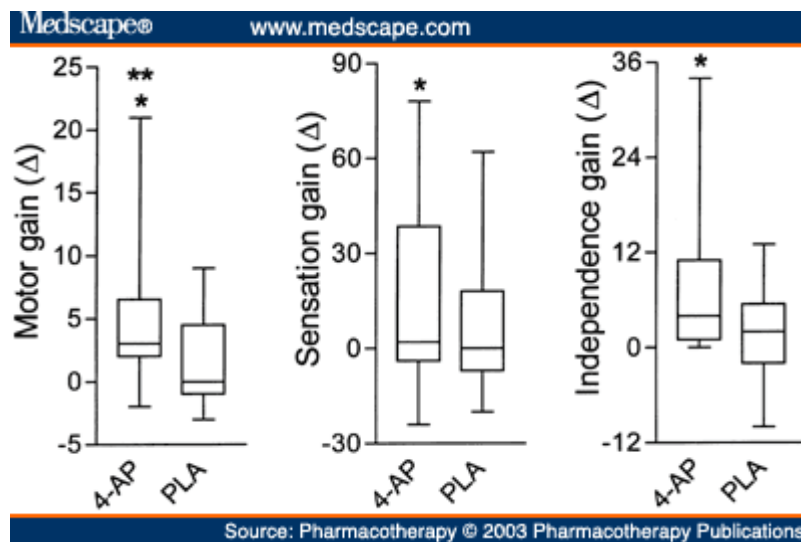


Figure 2. Functional response to 4-aminopyridine (4-AP) and placebo (PLA) after 12 weeks of treatment. Differences (Δ) between pretreatment and after 12 weeks of 4-AP administration were plotted for each scale used. *Success in all scales, 4-AP versus placebo (χ^2 , $p=0.042$). **Success in motor scale, 4-AP versus placebo (Fisher exact test, $p=0.03$). Boxes represent the distribution of the data extending from the 25th-75th percentile; the line is drawn at the median. Whiskers represent the highest and lowest values.

In the 4-AP group with AIS grade B+ cervical and thoracic injuries, discrete motility of the affected muscles was observed; in three patients the improvement was remarkable, and their AIS grade was changed to C. In patients with AIS grades of C and D, enhancement in strength was noted in partially preserved functional muscles, as well as gains in movement in previously nonfunctioning muscles. All patients achieved endurance levels higher than during the pretreatment period in several activities (e.g., wheelchair self-transport, arm and leg rehabilitation exercises, and ambulation), experienced decreased fatigue, and had better recovery (in less time).

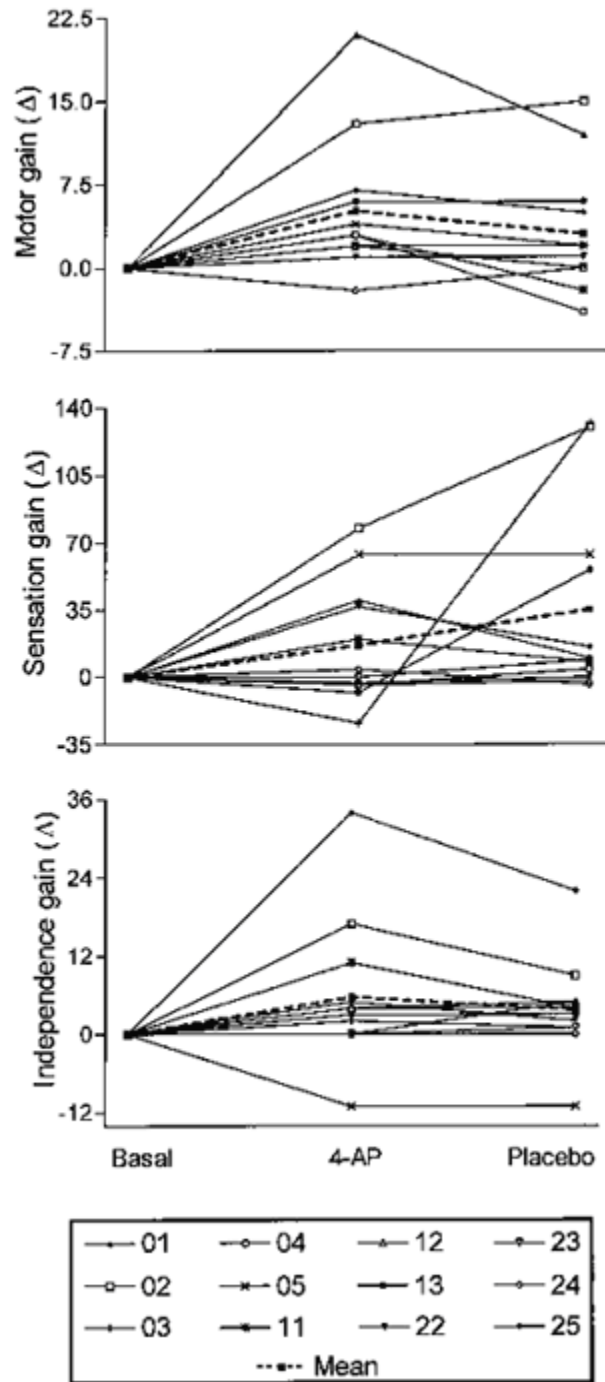
Sensation success rate was similar in both groups (4-AP 50% [6/12 patients] vs placebo 38% [5/13]); no significant differences were noted (Fisher exact test, $p=0.70$; Figure 2). Patients could discriminate presence or absence and laterality (left or right side) but not type and exact place of the stimuli; these sensations were insufficient to be quantified.

Finally, in the independence test, the 4-AP group achieved a higher success rate (67% [8/12 patients]), than the placebo group (54% [7/13]), but this difference did not reach statistical significance (Fisher's exact test, $p=0.69$; Figure 2).

The high response in the placebo group is noteworthy; evaluations indicated several patients who experienced success in motor function (46% [6/13 patients]), sensation (38% [5/13]), and independence (54% [7/13]). This was true for patients with incomplete injuries, and especially for those with complete injuries.

Persistent Effect of 4-AP After Discontinuation

A persistent 4-AP effect after drug discontinuation was observed in several patients. Five experienced a small loss of their 4-AP improvement beginning 3-4 days after they started taking placebo and mainly 1 week after 4-AP discontinuation, but no others felt this change. One 4-AP patient was partially impaired during the first 2 weeks of placebo treatment (especially in muscle strength). However, he then improved progressively to reach higher scores on both motor and sensory tests at the end of his placebo treatment period compared with scores at the end of his 4-AP treatment period; differences before and after treatment were significant. In 8 (67%) patients, preserved function of sensation was 6-100% ($p=0.032$). Surprisingly, sensation improved an average of 49% compared with scores at the end of 4-AP intake (Figure 3). Ten (83%) patients experienced persistent improvement in independence of 2-25% ($p=0.042$; Figure 3). Finally, seven patients preserved a 4-AP effect of 1-24% on motor function, but this was not significant ($p=0.098$; Figure 3).



Source: Pharmacotherapy © 2003 Pharmacotherapy Publications

Figure 3. Persistent 4-aminopyridine (4-AP) behavioral effect after 12 weeks of discontinuation. Patients who received 4-AP in the first treatment period were evaluated 12 weeks after 4-AP discontinuation (placebo period), at the end of the second study period (i.e., 24 wks of continuous treatment). Differences (Δ) between pretreatment and final scores are shown. The solid lines represent the results for each patient; the dotted lines represent the mean. Significant differences were demonstrated in evaluations of sensation and independence (Wilcoxon signed rank test, $p=0.032$ and $p=0.042$, respectively).

4-AP Responders

Analysis of a single patient response allowed us to identify consistent functional improvement in some patients after 4-AP treatment but not with placebo. All those who started in the 4-AP group experienced improvement in one of the three areas tested, and three improved consistently on all three scales. The three 4-AP patients who responded well also achieved a significant increase in their scores, higher than the mean of their group at least in two of the three scales. Two of these three patients were aged 23 years, and their postinjury time was less than 2.5 years. Two patients had a closed injury (car and sporting accidents, respectively) at the cervical level. Finally, two had injuries of AIS grade B+, which was changed to C at the end of the 4-AP period (and at the completion of the study).

Safety

Fifty-six probable adverse reactions were registered; these were observed in one of the excluded patients and in 20 who completed the study. Fourteen patients receiving 4-AP treatment had 26 probable adverse reactions. No epileptic seizures occurred. The excluded patient had a moderate adverse reaction characterized by posterior tibial artery vasospasm while receiving 4-AP 20 mg/day. This patient was hospitalized and successfully treated with an oral calcium antagonist (nifedipine 30 mg/day) with complete recovery. The other 25 probable adverse reactions were mild, thus it was not necessary to alter the blind study design to change dosing ([Table 2](#)).

Using a published algorithm^[31] to classify the 26 suspected adverse reactions in the 4-AP patients, 3 were definitive, 20 probable, 1 possible, and 2 doubtful. The adverse reactions appeared from the beginning of the weekly dosage increases and from 15-45 minutes after taking 4-AP. They generally resolved within 1-4 hours after taking 4-AP and disappeared within 3-5 days of continuous treatment. Dry mouth, dizziness, and gastritis began with 4-AP 5 or 10 mg/day; oral and peripheral paresthesia appeared only with 4-AP 30 mg/day.

Blood tests did not show any significant effects of 4-AP on renal function and electrolyte balance, but showed some mild effects on hematologic parameters and enzyme levels. Six patients had increased enzyme levels, and one had mild thrombocytopenia (platelet count $115-135 \times 10^3/\text{mm}^3$; [Table 3](#)). Abnormal enzyme levels never were higher than 2 times the upper limit of normal levels and diminished gradually. Both enzyme and platelet alterations resolved during 4-AP treatment or within 8 weeks after drug discontinuation.

Discussion

Between the time of a 1993 study that observed restored toe movements and enhanced volitional electromyographic interference patterns^[22] and a 2002 study that demonstrated significant changes in cardiac function,^[33] several studies reported that after treatment

with 4-AP, improvement occurred in motor control, gait, increased stability, foot clearance, coordination, endurance, stair climbing, wheelchair transfer, and manual dexterity.^[3, 21-28] On the other hand, one study found no significant improvement in functional status and ability to walk, and found only partial significant gain in vibration sensation.^[4]

Global improvement such as that seen in the present work has not been reported in previous controlled trials of 4-AP, perhaps due to the use of different scales or the complexity of each scale and inability to use a mixture of homogeneous scores. Using success or failure, although a gross measure, is a simple method for evaluating outcome. Moreover, it can allow the use of several scales together as a comparative index.

In spite of this global improvement, it is important to compare and discuss the evaluations of motor function, sensation, and independence obtained in this work as separate results. As in a previous study,^[3] our results regarding motor function show significant differences but conflict with the findings of another study.^[4] This discordance may be due to several causes.

The first possible cause is the AIS grading system. The injuries of most (13/19) patients in one study^[4] were graded D; in another study^[3] 12 injuries were graded C, 11 were graded D, and six were graded B. In our present work 10 injuries were graded B and six C. This is relevant because some of our patients with grade B injuries showed the greatest improvement. Poorer functionality in patients with lower AIS-grade injuries could be due not only to fewer preserved axons, but also to persistent demyelination. If that is true, 4-AP treatment results in improved behavioral scores.

The second possible cause of discordance among study results concerns the evaluation of motor function. One study^[4] used the Comfortable and Maximum Walking Speed Assessment; another study^[3] and our present work used the ASIA motor test. Use of similar evaluation techniques might yield more consistent results.

A third possible cause concerns dosing differences. One study administered lower dosages (4-AP 17.5 mg/day),^[3] we administered intermediate dosages (4-AP 5-30 mg/day), and another study administered higher dosages (4-AP 15-45 mg/day).^[4] Experimental models of SCI demonstrate that dosing influences functional response. By changing the 4-AP concentrations (for bath application of 4-AP) from 0.5-100.0 μ M, the amplitude of the compound action potential increased, but with higher 4-AP concentrations (1-10 mM), conduction was suppressed.^[13, 14] The fact that an increase in dosing may diminish the beneficial effect of 4-AP could explain, at least partially, the lack of significant differences in this study's results.^[4] However, a 1993 study proposed that the modest changes in electrophysiologic and clinical function could be attributable to the conservative doses of drug,^[22] and a 1998 study proposed increasing 4-AP dosing in an effort to derive maximum benefit.^[3] This possibility should be explored more extensively.

Improved sensation has been frequently shown as a 4-AP measurement of behavioral

response to 4-AP.^[3, 21-23, 26, 27] One study demonstrated significant differences in sensation (light touch and pinprick) in patients receiving 4-AP therapy compared with those receiving placebo,^[3] and one study noted significant statistical differences only partially (during the first study period) in threshold of vibration perception.^[4] In the present work, despite the fact that scores were better for patients receiving 4-AP therapy, no significant differences were noted when compared with placebo.

Two possibilities must be considered here. The sensory ordinal scale used, which has only three grades for functionality, did not allow discrimination of small changes in the present work. Several patients perceived some stimuli after 4-AP treatment, but they could not discriminate stimuli in sufficient detail (type and exact place) to be quantified. The other possibility is the placebo effect. The role of placebo in medicine has been recognized for many years.^[34, 35] Placebos have demonstrated healing effects in patients with angina pectoris,^[36] epilepsy,^[37] cancer,^[38] and even Parkinson's disease.^[39] In the present work, patients receiving placebo improved by 38-54% in evaluations of motor function, sensation, and independence. The placebo effect was seen in our patients, with both complete and incomplete SCI.

Some previous noncontrolled studies showed changes on independence measures, but none of the controlled trials have shown significant differences when compared with placebo in this kind of evaluation. The functional independence measure,^[3] the functional status measure,^[4] and the independence scale in our work did not demonstrate differences. The soft data obtained with questionnaires are weaker than other harder, more objective assessment methods.^[40] Despite the clarity of the items, correct researcher interpretation, and researcher consistency, tests may be influenced by patients' state of mind and their expectations of drug improvement, as well as the researchers' expectations.

4-AP Responders

Some aspects of patients who responded to 4-AP therapy support better recovery. One is the AIS grading system. A second aspect is level of injury. Based on experimental studies showing that 5-10% of preserved spinal cord axons support substantial residual neurologic function,^[17] cervical injury could have a better chance of some improvement. A third aspect is age. In newborn animals, collateral axon sprouting in the spinal cord is extensive with lesions and decreases with increasing age.^[41] In younger human patients with SCI, plasticity phenomena could be stronger than in older patients. This could involve some dynamic reorganization of the motor cortex, as seen in remission of multiple sclerosis.^[42]

A fourth aspect is postinjury time. After the acute SCI phase, the preserved axons can be unmyelinated or insufficiently myelinated. These axons will be progressively myelinated,^[7] and the long-term myelination could support additional improvement. 4-Aminopyridine therapy could then allow early functioning of these abnormally myelinated axons. A fifth aspect concerns closed SCI. Patients whose injuries resulted from motor vehicle accidents have higher recovery rates than those injured by

gunshots,^[43] who incur significantly more paraplegia and complete SCI.^[44]

These aspects of patients with SCI who respond well to 4-AP therapy, however, do not preclude a good response from other patients with different kinds of lesions.

Long-Term Effect of 4-AP Treatment

Some authors have reported that a single intravenous dose of 4-AP induces a transient neurologic gain from the time of drug administration to 24-48 hours later.^[21, 22] Oral long-term 4-AP intake has maintained benefits for 1-2 weeks.^[26, 27] Surprisingly, in the present study, not only did the patients show persistent beneficial effects of 4-AP during the 12 weeks after drug discontinuation, but some patients also improved in both motor function and sensation. Enterosystemic recirculation of 4-AP^[21, 27] or gastric dysfunction^[45] in patients with SCI has been hypothesized to explain the persistent effect of 4-AP therapy, which can last for several hours-2 weeks. Also, in patients with SCI, 4-AP has a long half-life of about 18 hours.^[27]

However, these 4-AP bioavailability alterations are insufficient to explain its persistent effect for as long as 12 weeks. Unidentified mechanisms, such as sequestration of active drug by the central nervous system, altered synaptic mechanisms, and changes in the number, molecular configuration, and sensitivity of axonal ion channels have been hypothesized to explain this phenomenon.^[26] Another explanation for this long-term effect could be that 4-AP drives some plasticity phenomena, similar to extracellular purines and pyrimidines on neurons and glial cells.^[46-48] These hypotheses must be supported by further research.

Safety

Serious adverse reactions (e.g., epileptic seizures, severe laboratory-determined abnormalities) were not encountered during this study. This might be due to our dosage scheme, which allowed a maximum daily dosage of 4-AP 0.6 mg/kg of body weight. Almost all adverse reactions were mild, brief, and transitory, and they were similar to those reported previously in patients with SCI and other diseases.^[3, 21, 22, 25-27, 49-52] No patient required dosage reduction. However, we observed additional adverse reactions that had not been previously reported, such as memory alteration, bitter taste in the mouth, global pinching pain, and cramps. Enzyme and platelet alterations were transitory, and resolved during the 4-AP treatment period or after drug discontinuation. Only one moderate adverse reaction - arterial vasospasm - occurred, and the patient recovered completely. Similar adverse reactions have been reported but they were with the intravenous preparation of 4-AP.^[22] One patient received the first dose of 4-AP by means of an unsuccessful venipuncture; then local vasoconstriction occurred, with blanching and cooling of the forearm.

Conclusion

4-Aminopyridine improved neurologic function in patients with long-term SCI. Despite

the fact that 4-AP therapy can improve motor function, sensation, and independence, improved motor function was consistent when patients were receiving the drug and impaired after discontinuation. Patients with incomplete SCI (AIS grades B and C), youth, short postinjury time, cervical level of injury, and closed SCI had better functional response. 4-Aminopyridine has a persistent effect after 12 weeks of its discontinuation. It is a safe drug, with only mild and tolerable adverse reactions, and transitory enzyme and platelet alterations. However, in patients receiving 4-AP 30 mg/day, platelet counts and serum enzyme levels (ALT, AST, ALP, and CK) should be monitored, and patients should be monitored for possible arterial vasospasms and other mild adverse reactions such as dry mouth, dizziness, nausea, gastritis, and oral and peripheral paresthesia.

Tables

Table 1. Patient Demographics and Spinal Cord Injury Characteristics

	Sex	Age (yrs)	Postinjury Time (yrs)	Cause of Injury	Injury Level	AIS Grade
4-AP-placebo sequence						
	M	48	10.0	MVA	C4	B+
	M	31	7.0	MVA	C4	B+
	F	33	10.0	MVA	C4	B+
	M	43	15.0	MVA	C5	D
	M	23	1.5	Diving	C5	B+
	M	29	3.0	Diving	C6	C
	M	31	13.0	Gunshot	T4	C
	F	44	6.0	Gunshot	T5	C
	M	35	9.0	Gunshot	T5	B
	M	27	8.0	MVA	T6	B+
	M	42	6.0	MVA	T6	B+
	M	23	2.5	Gunshot	T7	C
Mean ± SD		34 ± 8.4	7.6 ± 4.3			
Placebo-4-AP sequence						
	M	35	7.0	Diving	C4	C
	M	40	10.0	MVA	C4	A+
	M	40	5.0	MVA	C5	B+
	M	25	6.0	Fall	C5	B+
	M	42	7.0	Fall	T1	D

	M	26	4.0	Gunshot	T2	C
	M	44	6.0	Gunshot	T2	B
	M	24	7.0	MVA	T4	B+
	F	30	11.0	MVA	T5	A
	M	29	5.0	MVA	T6	D
	F	25	7.0	Fall	T8	B+
	M	24	6.0	Gunshot	T9	B+
	M	42	5.0	Fall	T11	A+
Mean ± SD		33 ± 7.9	6.6 ± 2.0			

4-AP = 4-aminopyridine; AIS = American Spinal Cord Injury Association impairment scale; MVA = motor vehicle accident; C = cervical; T = thoracic.

Table 2. Adverse Reactions in Patients with Long-Term Spinal Cord Injury Receiving 4-Aminopyridine and Placebo

Adverse Reaction	4-Aminopyridine		Placebo
	No. of Patients	Dosage Range (mg/day)	No. of Patients
Dry mouth	5	5-30	3
Dizziness	3	5-30	4
Nausea	3	15-30	4
Gastritis	3	10-30	1
Paresthesia (oral and peripheral)	3	30	2
Arterial vasospasm ^a	1	20	0
Insomnia, anxiety, headache, cramps, memory alterations, increased viscosity of saliva, bitter taste in mouth, global pinching pain	8	5-30	9
Diaphoresis, abdominal distention, abdominal pain, phosphenes, hyperphagia, itchy eyes	0	-	7

^aModerate adverse reaction resolved with no sequelae.

Table 3. Dosing and Time of Presentation and Resolution of Alterations in Laboratory Values of Six Patients with Long-Term Spinal Cord Injury Receiving 4-Aminopyridine for 12 Weeks

Laboratory Alteration ^a	4-AP Daily Dose (mg)	Time of Presentation (wks)	Week of Resolution and Status of 4-AP
↑ALT, ↑AST, ↑ALP	30	8	4th after discontinuation ^b
↑ALT, ↑AST	30	8	8th after discontinuation ^b
↑ALT	20	4	4th after discontinuation ^c
↑ALT, ↑AST, ↑ALP	30	8	12th during treatment ^d
↑CK	30	8	4th after discontinuation ^c
↑ALT	20	4	8th during treatment ^d
↓Platelet count	20	4	8th after discontinuation ^c

4-AP = 4-aminopyridine, ALT = alanine aminotransferase; AST = aspartate aminotransferase; ALP = alkaline phosphatase; CK = creatine kinase.

^aAlterations in enzyme levels were never higher than 2 times the upper limit of the normal range. Platelet counts ranged from 115-135 x 10³/mm³.

^bResolution of the alteration was during the second period of treatment in which patients were taking placebo.

^cResolution of the alteration was after the end of the study, when patients did not receive the drug.

^dResolution of the alteration was during 4-AP intake.

References

1. Bracken MB, Shepard MJ, Collins WF, et al. A randomized, controlled trial of methylprednisolone or naloxone in the treatment of acute spinal cord injury: results of the second national acute spinal cord injury study. *N Engl J Med* 1990;322:1405-11.
2. Coleman WP, Benzel D, Cahill DW, et al. A critical appraisal of the reporting of the national acute spinal cord injury studies (II and III) of methylprednisolone in acute spinal cord injury. *J Spinal Disord* 2000;13:185-99.
3. Potter PJ, Hayes KC, Segal JL, et al. Randomized double-blind crossover trial of

- fampridine-SR (sustained release 4-aminopyridine) in patients with incomplete spinal cord injury. *J Neurotrauma* 1998;15:837-49.
4. van der Bruggen MA, Huisman HB, Beckerman H, Bertelsmann FW, Polman CH, Lankhorst GJ. Randomized trial of 4-aminopyridine in patients with chronic incomplete spinal cord injury. *J Neurol* 2001;248:665-71.
 5. Blight AR. Delayed demyelination and macrophage invasion: a candidate for secondary cell damage in spinal cord injury. *Cent Nerv Syst Trauma* 1985;2:299-315.
 6. Blight AR, Decrescito V. Morphometric analysis of experimental spinal cord injury in the cat: the relation of injury intensity to survival of myelinated axons. *Neuroscience* 1986;19:321-41.
 7. Salgado-Ceballos H, Guizar-Sahagun G, Feria-Velasco A, et al. Spontaneous long-term remyelination after traumatic spinal cord injury in rats. *Brain Res* 1998;782:126-35.
 8. Sherratt RM, Bostock H, Sears TA. Effects of 4-aminopyridine on normal and demyelinated mammalian nerve fibres. *Nature* 1980;283:570-2.
 9. Blight AR, Gruner JA. Augmentation by 4-aminopyridine of vestibulospinal free fall responses in chronic spinal-injured cats. *J Neurol Sci* 1987;82:145-59.
 10. Blight AR. Effect of 4-aminopyridine on axonal conduction-block in chronic spinal cord injury. *Brain Res Bull* 1989;22:47-52.
 11. Blight AR, Toombs JP, Bauer MS, Widmer WR. The effects of 4-aminopyridine on neurological deficits in chronic cases of traumatic spinal cord injury in dogs: a phase I clinical trial. *J Neurotrauma* 1991;8:103-19.
 12. Waxman SG. Aminopyridines and the treatment of spinal cord injury. *J Neurotrauma* 1993;10:19-24.
 13. Shi R, Blight AR. Differential effects of low and high concentrations of 4-aminopyridine on axonal conduction in normal and injured spinal cord. *Neuroscience* 1997;77:553-62.
 14. Shi R, Kelly TM, Blight AR. Conduction block in acute and chronic spinal cord injury: different dose-response characteristics for reversal by 4-aminopyridine. *Exp Neurol* 1997;148:495-501.
 15. Gruner JA, Yee AK. 4-Aminopyridine enhances motor evoked potentials following graded spinal cord compression injury in rats. *Brain Res* 1999;816:446-56.
 16. Bunge RP, Puckett WR, Becerra JL, Marcillo A, Quencer RM. Observations on the pathology of human spinal cord injury: a review and classification of 22 new cases with details from a case of chronic cord compression with extensive focal demyelination. *Adv Neurol* 1993;59:75-89.
 17. Blight AR. Cellular morphology of chronic spinal cord injury in the cat: analysis of myelinated axons by line-sampling. *Neuroscience* 1983;10:521-43.
 18. Lundh H, Thesleff S. The mode of action of 4-aminopyridine and guanidine on transmitter release from motor nerve terminals. *Eur J Pharmacol* 1977;42:411-12.
 19. Smith KJ, Felts PA, John GR. Effects of 4-aminopyridine on demyelinated axons, synapses and muscle tension. *Brain* 2000;123:171-84.
 20. Yu K, Rong W, Li J. Neurophysiological evidence of spared upper motor conduction fibers in clinically complete spinal cord injury: discomplete SCI in

- rats. *J Neurol Sci* 2001;189:23-36.
21. Hansebout RR, Blight AR, Fawcett S, Reddy K. 4-Aminopyridine in chronic spinal cord injury: a controlled, double-blind, crossover study in eight patients. *J Neurotrauma* 1993;10:1-18.
 22. Hayes KC, Blight AR, Potter PJ, et al. Preclinical trial of 4-aminopyridine in patients with chronic spinal cord injury. *Paraplegia* 1993;31:216-24.
 23. Hayes KC, Potter PJ, Wolfe DL, Hsieh JT, Delaney GA, Blight AR. 4-Aminopyridine-sensitive neurologic deficits in patients with spinal cord injury. *J Neurotrauma* 1994;11:433-46.
 24. Qiao J, Hayes KC, Hsieh JT, Potter PJ, Delaney GA. Effects of 4-aminopyridine on motor evoked potentials in patients with spinal cord injury. *J Neurotrauma* 1997;14:135-49.
 25. Segal JL, Brunnemann SR. 4-Aminopyridine alters gait characteristics and enhances locomotion in spinal cord injured humans. *J Spinal Cord Med* 1998;21:200-4.
 26. Segal JL, Pathak MS, Hernandez JP, Himber PL, Brunnermann SR, Charter RS. Safety and efficacy of 4-aminopyridine in humans with spinal cord injury: a long-term, controlled trial. *Pharmacotherapy* 1999;19:713-23.
 27. Potter PJ, Hayes KC, Hsieh JT, Delaney GA, Segal JL. Sustained improvements in neurological function in spinal cord injured patients treated with oral 4-aminopyridine: three cases. *Spinal Cord* 1998;36:147-55.
 28. Wolfe DL, Hayes KC, Hsieh JT, Potter PJ. Effects of 4-aminopyridine on motor evoked potentials in patients with spinal cord injury: a double-blinded, placebo-controlled crossover trial. *J Neurotrauma* 2001;18:757-71.
 29. Maynard FM Jr, Bracken MB, Creasey G, et al. International standards for neurological and functional classification of spinal cord injury. American Spinal Injury Association. *Spinal Cord* 1997;35:266-74.
 30. Catz A, Itzkovich M, Agranov E, Ring H, Tamir A. SCIM-spinal cord independence measure: a new disability scale for patients with spinal cord lesions. *Spinal Cord* 1997;35:850-6.
 31. Karch FE, Lasagna L. Toward the operational identification of adverse drug reactions. *Clin Pharmacol Ther* 1977;21:247-54.
 32. Sumida M, Fujimoto M, Tokuhiko A, Tominaga T, Magara A, Uchida R. Early rehabilitation effect for traumatic spinal cord injury. *Arch Phys Med Rehabil* 2001;82:391-5.
 33. Segal JL, Warner AL, Brunnermann SR, Bunten DC. 4-aminopyridine influences heart rate variability in long-standing spinal cord injury. *Am J Ther* 2002;9:29-33.
 34. de Craen AJ, Kaptchuk TJ, Tijssen JG, Kleijnen J. Placebos and placebo effects in medicine: historical overview. *J R Soc Med* 1999;92:511-15.
 35. Thompson WG. Placebos: a review of the placebo response. *Am J Gastroenterol* 2000;95:1637-43.
 36. Benson H, McCallie DP Jr. Angina pectoris and the placebo effect. *N Engl J Med* 1979;300:1424-9.
 37. Anonymous. Gabapentin in partial epilepsy: UK gabapentin study group. *Lancet* 1990;333:1114-17.
 38. Downer SM, Cody MM, McCluskey P, et al. Pursuit and practice of

- complementary therapies by cancer patients receiving conventional treatment. *BMJ* 1994;309:86-9.
39. Stoessel AJ. Neurochemical and neuroreceptor imaging with PET in Parkinson's disease. *Adv Neurol* 2001;86:215-23.
 40. Feinstein AR. An additional basic science for clinical medicine: IV. The development of clinimetrics. *Ann Intern Med* 1983;99:843-8.
 41. Kapfhammer JP. Axon sprouting in the spinal cord: growth promoting and growth inhibitory mechanisms. *Anat Embryol (Berl)* 1997;196:417-26.
 42. Reddy H, Narayanan S, Matthews PM. Relating axonal injury to functional recovery in MS. *Neurology* 2000;54:236-9.
 43. Velmahos GC, Degiannis E, Hart K, Souter I, Saadia R. Changing profiles in spinal cord injuries and risk factors influencing recovery after penetrating injuries. *J Trauma* 1995;38:334-7.
 44. McKinley WO, Johns JS, Musgrove JJ. Clinical presentations, medical complications, and functional outcomes of individuals with gunshot wound-induced spinal cord injury. *Am J Phys Med Rehabil* 1999;78:102-7.
 45. Segal JL, Milne N, Brunnemann SR. Gastric emptying is impaired in patients with spinal cord injury. *Am J Gastroenterol* 1995;90:466-70.
 46. Abbracchio MP, Saffrey MJ, Hopker V, Burnstock G. Modulation of astroglial cell proliferation by analogues of adenosine and ATP in primary cultures of rat striatum. *Neuroscience* 1994;59:67-76.
 47. Neary JT, Baker L, Jorgensen SL, Noremborg MD. Extracellular ATP induces stellation and increases glial fibrillary acidic protein content and DNA synthesis in primary astrocyte cultures. *Acta Neuropathol (Berl)* 1994;87:8-13.
 48. Neary JT, Rathbone MP, Cattabeni F, Abbracchio MP, Burnstock G. Trophic actions of extracellular nucleotides and nucleosides on glial and neuronal cells. *Trends Neurosci* 1996;19:13-18.
 49. Murray NM, Newsom-Davis J. Treatment with oral 4-aminopyridine in disorders of neuromuscular transmission. *Neurology* 1981;31:265-71.
 50. Van Diemen HA, Polman CH, Koetsier JC, Van Loenen AC, Nauta JJ, Bertelsmann FW. 4-Aminopyridine in patients with multiple sclerosis: dosage and serum level related to efficacy and safety. *Clin Neuropharmacol* 1993;16:195-204.
 51. van Diemen HA, Polman CH, van Dongen TM, et al. The effect of 4-aminopyridine on clinical signs in multiple sclerosis: a randomized, placebo-controlled, double-blind, cross-over study. *Ann Neurol* 1992;32:123-30.
 52. Segal JL, Brunnemann SR. 4-Aminopyridine improves pulmonary function in quadriplegic humans with longstanding spinal cord injury. *Pharmacotherapy* 1997;17:415-23.

Acknowledgements

The authors thank Dr. Patrick Wood, Maria Oliveira, and Susan Holmes for their helpful revision of the manuscript, and Proyecto Camina A.C., Laura Baldwin, and Luis Gonzalez for their help when it was necessary. Special thanks to Dr. Jack L. Segal and

work.

Funding Information

Supported by Instituto Mexicano del Seguro Social and Centro de Investigación y Estudios Avanzados, Instituto Politécnico Nacional.

Reprint Address

Address reprint requests to Israel Grijalva M.D., Ph.D., Calzada de Tlapan 4430, Col. Toriello Guerra, CP 14050, México, DF, México; e-mail: igrijalvao@yahoo.com.

From the Research Medical Unit for Neurological Diseases, Specialties Hospital (**Drs. Grijalva, Guízar-Sahagún, Maldonado-Julián, Ibarra, Serra, and Salgado-Ceballos**), and Health Research Coordination (**Dr. Mino**), Centro Médico Nacional Siglo XXI, Instituto Mexicano del Seguro Social; the Pharmacology and Toxicology Department (**Dr. Castañeda-Hernández** and **Ms. Vidal-Cantú**) and the Pharmacology External Section (**Ms. Arenas-Hernández**), Centro de Investigación y Estudios Avanzados, Instituto Politécnico Nacional, México City, México.
