Safety and Efficacy of 4-Aminopyridine in Humans with Spinal Cord Injury: A Long-Term, Controlled Trial

Jack L. Segal, M.D., FACP, FCP, Mayank S. Pathak, M.D., Jesus P. Hernandez, M.D., Peter L. Himber, M.D., Sherry R. Brunnemann, B.S., and Richard S. Charter, Ph.D.

Pharmacotherapy 19(6):713-723, 1999.

Abstract and Introduction

Abstract

Study Objective. To determine the effects of the long-term administration of 4-aminopyridine (4-AP) on sensorimotor function in humans with long-standing spinal cord injury (SCI).

Design. Randomized, open-label, active-treatment control, dosage-blinded study.

Setting. University-affiliated, tertiary-level care, Department of Veterans Affairs Medical Center.

Patients. Twenty-one healthy men and women outpatients suffering from traumatic SCI (14 tetraplegic, 7 paraplegic) for 2 years or more.

Interventions. Dosages of an immediate-release formulation of 4-AP were titrated. At 3 months, 16 subjects were receiving 4-AP 30 mg/day (high dose); 5 subjects were receiving 4-AP 6 mg/day (low dose) and served as an active-treatment control group.

Measurements and Main Results. Composite motor and sensory scores had statistically significant increases at 3 months. Maximal expiratory pressure, maximal inspiratory pressure, forced vital capacity, and forced expiratory volume in 1 second showed clinically meaningful and/or statistically significant increases among patients receiving 4-AP 30 mg/day. These subjects also had significant decreases in spasticity (modified Ashworth Scale). Serial biochemical profiles and electroencephalographs were

unchanged from baseline, and no clinically significant drug toxicity was encountered.

Conclusions. Long-term oral administration of immediate-release 4-AP was associated with improvement in and recovery of sensory and motor function, enhanced pulmonary function, and diminished spasticity in patients with long-standing SCI. 4-Aminopyridine appears to be safe and relatively free from toxicity when administered orally over 3 months. Each patient who received immediate-release 4-AP 30 mg/day showed a response in one or more of the outcome measures.

Introduction

Since the first written description of traumatic tetraplegia appeared in an ancient Egyptian papyrus, traumatic spinal cord injury (SCI) has essentially remained "an ailment not to be treated."[1] Even in modern times, the human spinal cord remains refractory to pharmacologic manipulation, particularly with respect to its function as an integrator or modulator of volitional motor function and sensory perception. Nevertheless, several decades of advances in pharmacotherapy, surgery, and rehabilitation medicine have contributed to ameliorating the myriad pathophysiolgic sequelae of SCI, increasing longevity, and enhancing the recovery of physiologic homeostasis. Only recently has a central nervous system (CNS)-active agent capable of causing improvement in sensorimotor function in humans been introduced.[2-4]

Spinal cord trauma and its sequelae are only rarely associated with a complete anatomic transection. In most patients, some degree of axonal continuity persists, and translesional propagation of action potentials is preserved in varying degree. Extensive intralesional demyelination resulting in conduction block, however, is common,[5-7] and a drug effective in overcoming or attenuating the block could be valuable. Experience with 4-aminopyridine (4-AP) shows it to be a CNS-active agent with this property.[7, 8]

4-Aminopyridine is a voltage-gated, fast potassium channel blocker capable of improving axonal conduction by facilitating the propagation of action potentials in demyelinated nerve fibers.[7, 8] It also influences neurologic function in intact animal models of SCI and in clinical conditions in which demyelination is a contributing factor to neurologic deficit.[2, 9-12] Data from human and animal studies suggest that locomotor function and sensory input are preserved after injury even though only a small proportion of neurons remains intact and viable. Clinically significant restoration of sensorimotor function can occur in the face of only modest recovery from severe neurologic impairment.[5, 11, 13, 14]

In a prior study, significant improvements in pulmonary function and respiratory muscle strength occurred in patients with SCI who were administered a single dose of 4-AP.[2] The present study was undertaken to test the validity of these findings and to assess the safety and efficacy of long-term administration of 4-AP in improving volitional motor function and enhancing sensory perception in a larger, more diversified cohort.

Methods

Subject Selection and Characteristics

The study was conducted with the approval of the U.S. Food and Drug Administration (FDA). Twenty-one healthy volunteers (18 men, 3 women; 14 tetraplegic, 7 paraplegic; Table 1) with traumatic SCI of more than 2 years' duration completed the study. They all provided institution-approved, written informed consent. Injuries were complete in 9 subjects and incomplete in 12.[15] Eleven subjects who were unexposed to 4-AP (4-AP naïve) were randomly assigned to receive high- or low-dose 4-AP. Ten subjects who had received 4-AP were unblinded and assigned to receive high-dose 4-AP (Figure 1). These subjects had participated in a short-term (24-hr) study of the effects of a single 10-mg dose and/or 2 weeks of 35 mg/day orally more than 1 year before the present study. All participants were followed for 3 months in a seasonally balanced, low-dose, active-drug controlled trial of 4-AP. Study subjects did not differ significantly in age, height, weight, or injury duration.

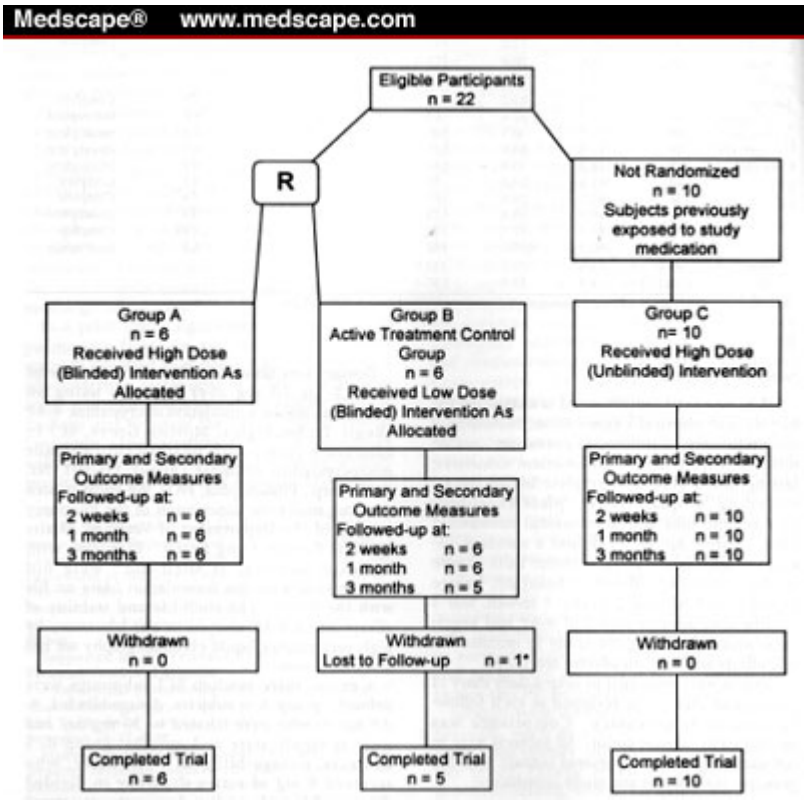

Figure 1. Flow diagram shows the progress of study participants through the clinical trial. R indicates randomization. *Data from this subject were omitted from statistical analysis.

The medical records of each prospective participant and their written responses to a detailed prescreening questionnaire were reviewed before the screening evaluation. Before enrolling, each participant underwent a comprehensive history and physical examination and detailed neurologic examination. Laboratory tests were electro-encephalogram (EEG), resting electrocardiogram (ECG), a comprehensive biochemical profile, a hematologic and blood clotting profile, urinalysis, a lipid panel, and a 5-hour

glucose tolerance test. In patients selected for enrollment, these examinations and tests were repeated at each scheduled visit or as necessary to rule out toxicity and document metabolic or physiologic alterations potentially attributable to 4-AP.

Exclusion criteria were epilepsy, seizures, or an abnormal EEG; recreational or illicit drug use, including ethanol abuse; maintenance treatment with bronchodilators; anticholinergic (atropinic) or antihistaminic drugs; psychiatric disorders; and pregnancy or inadequate or unverifiable gender-specific contraceptive measures.

Subjects were directed to continue their usual lifestyle, such as activity levels, sleep-wake cycles, and dietary patterns, for the duration of the study except when they returned for scheduled testing, which was defined, a priori, as time of day (circadian rhythm) and diet content-dependent.

Safety Measurements

Safety measurements consisted of a standardized history and physical examination, including a comprehensive neurologic examination; assess-ments of hepatic and renal function; urinalysis; fasting blood glucose; complete blood count, including a quantitative platelet count; prothrombin time and international normalized ratio; creatine kinase; EEG; and a standard 12-lead and ambulatory 24-hour Holter ECG. These studies were carried out at baseline, before exposure to 4-AP, and 2 weeks, 1 month, and 3 months after administration of 4-AP had begun or as necessary during the study to monitor for side effects and rule out adverse reactions.

Subjects were requested to keep a daily diary of events, and these were reviewed at each follow-up visit or as necessary. Compliance was monitored by capsule count. All subjects were in constant telephonic or personal contact with the principal investigator and study coordinator.

Interventions and Treatments

Dosages were titrated to tolerance in increments of 2, 5, or 10 mg over 2 weeks using an immediate-release formulation of crystalline 4-AP (Regis Technologies, Morton Grove, IL) in admixture (w/w) with pharmaceutical-grade microcrystalline cellulose (Avicel; PH-101, NF, FMC Corp., Philadelphia, PA). We encapsulated the drug under the supervision of the Pharmacy Service of the Department of Veterans Affairs Medical Center, Long Beach. Problems with stability, potency, or shelf-life[12] were not encountered with this formulation (data on file with the FDA). The shelf-life and stability of encapsulated 4-AP assayed in our laboratory by high-performance liquid chromatography are not less than 1 year.

A priori, three random SCI subgroups were defined: group A, 6 subjects, dosage-blinded, 4-AP naïve, who were titrated to 30 mg/day and were at steady state at 3 months; group B, 5 subjects, dosage-blinded, 4-AP naïve, who received 6 mg of active drug/day in divided doses, and served as a low-dose, active-treatment (control) subgroup; and group

C, 10 subjects, dosage-cognizant, who received 30 mg/day and were at steady state at 3 months. All subjects in group C had been exposed to 4-AP and could no longer be blinded.[2, 15] The trial incorporated an active-treatment control group rather than a placebo control (Figure 2).[16]

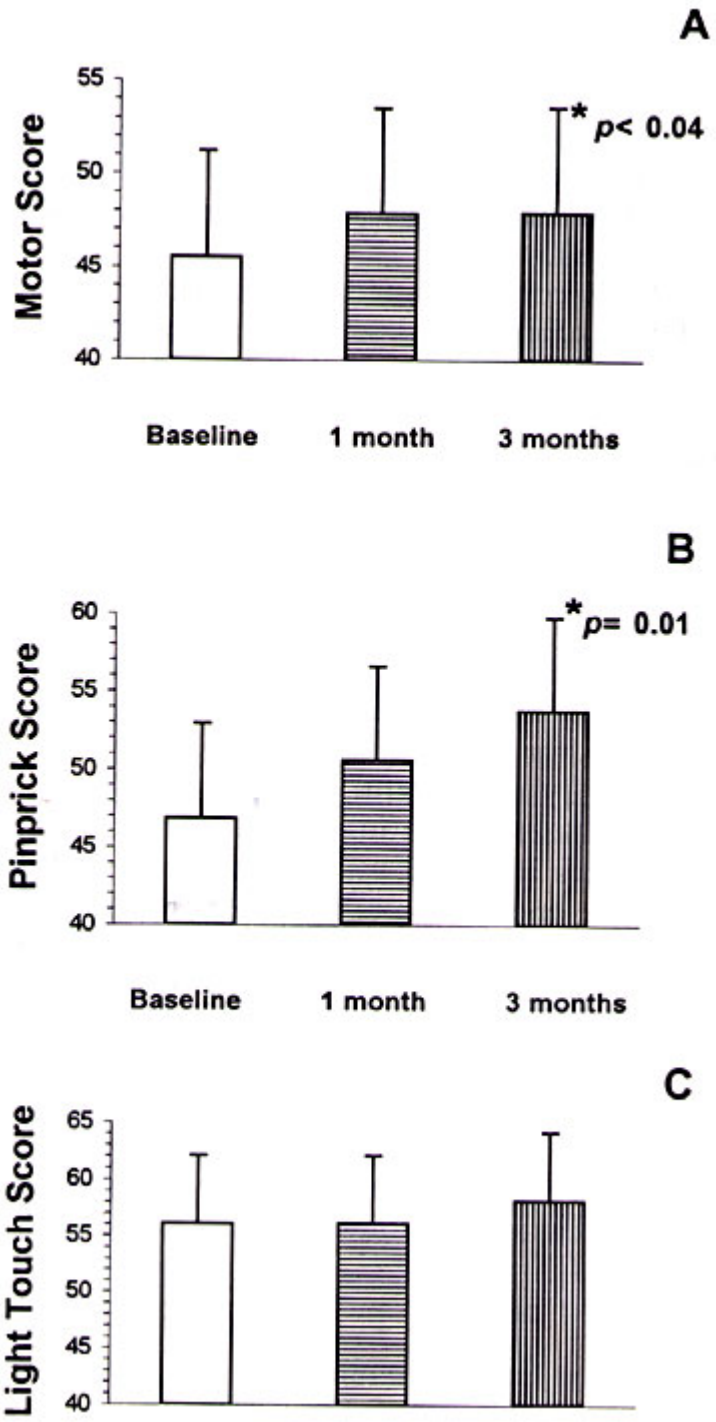

Figure 2. Primary outcome measures. (A) Motor score and (B) pinprick score (means ± SEM) showed statistically significant numeric increases among all study subjects at 3 months compared with baseline. Concomitant changes were not observed in the light touch score (C). Numeric increases in motor and pinprick scores were not observed in group B. The overall mean increase in numeric scores among all subjects corresponded to recovery of approximately 1.5 segmental levels. The functional significance or patient-perceived utility of these improvements remains to be determined.

Randomization

Individuals were randomized in accordance with a computer-generated allocation schedule. Allocation was concealed in sequentially numbered, sealed envelopes that were not opened until randomization, 1 day before enrollment.

Masking

All dosages were prepared using no. 2 gelatin capsules and microcrystalline cellulose. All capsules had the same appearance and taste, and did not perceptibly vary in weight. The investigational drug was stored and dispensed by the Pharmacy Service, and was issued in identical opaque plastic containers identified as containing 4-AP. Outcome assessors and data analysts were not informed of participants' dosage assignment, nor did they have access to the allocation schedule or code. The allocation schedule was kept by the research pharmacist throughout the study. It was not necessary to break the code at any time.

Primary Outcome Measurements

Changes in Neurologic and Functional Classification

Subjects were examined neurologically as specified elsewhere.[17] In this system of classification, motor strength testing is performed on 10 muscle groups on each side of the body, and each group is representative of a single segmental myotome. Each muscle group is assigned a motor strength score of 0-5, generating a unilateral score of 0-50, and these scores are summated to yield a total composite motor score of 0-100.

Sensory testing is performed on dermatomes C2 through S4-5 by light touch and pinprick. For each modality, the dermatome is assigned one of three scores: 0 = sensation absent, 1 = sensation present but impaired, and 2 = sensation normal. Thus, for each modality a sensory score of 0-56 is generated on each side of the body, yielding a summed composite score of 0-112 for pinprick sensation or light touch. On each side, the most caudal myotome and dermatome before an abnormality is detected were designated the motor and sensory spinal injury levels, respectively. The most caudal dermatome or myotome with partially preserved innervation was designated the zone of partial preservation (ZPP).

Motor impairment was classified as complete or incomplete based on the absence or presence of voluntary motor function at the external anal sphincter. Sensory impairment

was classified similarly based on the absence or presence of any sensation, including deep pressure, in the S4-5 dermatome (anal-perianal). Each examination and classification was conducted by a neurologist blinded to the dosage of 4-AP. The examinations were performed at baseline (pretreatment) and after 2 weeks, 1 month, and 3 months of active therapy. All subjects were examined when plasma concentrations of 4-AP were at steady state.

Pulmonary Function Tests

Pulmonary function tests (PFTs) were performed as described elsewhere.[2] Briefly, baseline measurements were obtained in triplicate, and predicted values were calculated from accepted formulas.[18] Maximal expiratory pressure (MEP), maximal inspiratory pressure (MIP), forced vital capacity (FVC), and forced expiratory volume in 1 second (FEV_1) were measured in triplicate at each follow-up visit using standard methods.[19]

Secondary Outcome Measurements

Modified Ashworth Scale

The modified Ashworth Scale[20, 21] was used to quantify skeletal muscle hypertonus. Subjects were evaluated at baseline and at each subsequent scheduled revisit. Limbs affected by SCI were passively manipulated through the range of motion of major joints, and a spasticity score of 0-4 was assigned.[20]

Other secondary outcome measurements were ZPP and change in classification (incomplete vs complete injury).

Statistical Analyses

Tests of the significance of the differences between means were carried out with analysis of variance (two-way, split-plot ANOVA) or an appropriate nonparametric analysis based on the $x^{[2]}$ statistic.[22] Normality of underlying distributions was tested using D'Agostino's Robust D test.

Clinically meaningful changes in pulmonary function tests, as distinguished from numerical or statistically significant increases, were defined using the convention adopted by the American Thoracic Society (ATS).[18] For each subject, standardized reference equations were used to calculate predicted FEV_1 or FVC as a function of chronologic age, height, and gender.[18]

A p value (two-tailed) of 0.05 or less was required to assign statistical significance to the difference between means or medians. Means are expressed as ± 1 SD unless otherwise indicated.

Results

Participant Flow and Follow-up

Figure 1 is a flow diagram that shows the progress of eligible patients through the study. All subjects were followed at 2 weeks, 1 month, and 3 months. One subject from group B relocated and declined to participate further, and this subject's data were excluded from the statistical analyses.

Primary Outcome Measures

Statistically significant recovery of sensorimotor function and improvements in functional classification were seen after 3 months of treatment with 4-AP. The mean composite motor score increased from 45.5 ± 26.1 to 47.9 ± 25.7 at 3 months in all 21 subjects ($p<0.04$; Figure 2). Because the between and interaction F ratios were nonsignificant, the magnitude of change in motor score at 3 months could be equally attributed to the variance contributed by each subgroup; that is, no statistically significant distinction could be made among their relative contributions. However, examination of subgroup means confirmed no increase in composite motor score attributable to the low-dose, dosage-blinded group.

The composite mean baseline score for perception of pinprick, 46.9 ± 27.0, increased by 15% to 53.8 ± 28.0 and attained statistical significance among all subjects at 3 months ($p=0.02$). Post hoc analysis showed that among all subjects, pinprick score was also significantly greater at 1 month than at baseline. A non-significant 5% improvement in perception of pinprick occurred at 3 months in group B. Comparison of individual subgroup mean scores, however, supported the inference that the increase in the mean composite score among all subjects at 1 and 3 months could be attributed to improved perception of pinprick in groups A and C.

No significant changes in light touch scores, the other sensory modality tested, were observed during 3 months of treatment with 4-AP, regardless of dosage achieved or blinding status. No drug tolerance (tachyphylaxis), carry-over, or altered responsivity to 4-AP was observed or anticipated in group C, as these subjects had had limited exposure to the drug more than 1 year before entering the present study.

Figures 3 and 4 show clinically meaningful (ATS criteria) and statistically significant improvements in pulmonary function and respiratory muscle strength. Changes were seen beginning as early as 2 weeks after starting treatment with 4-AP.

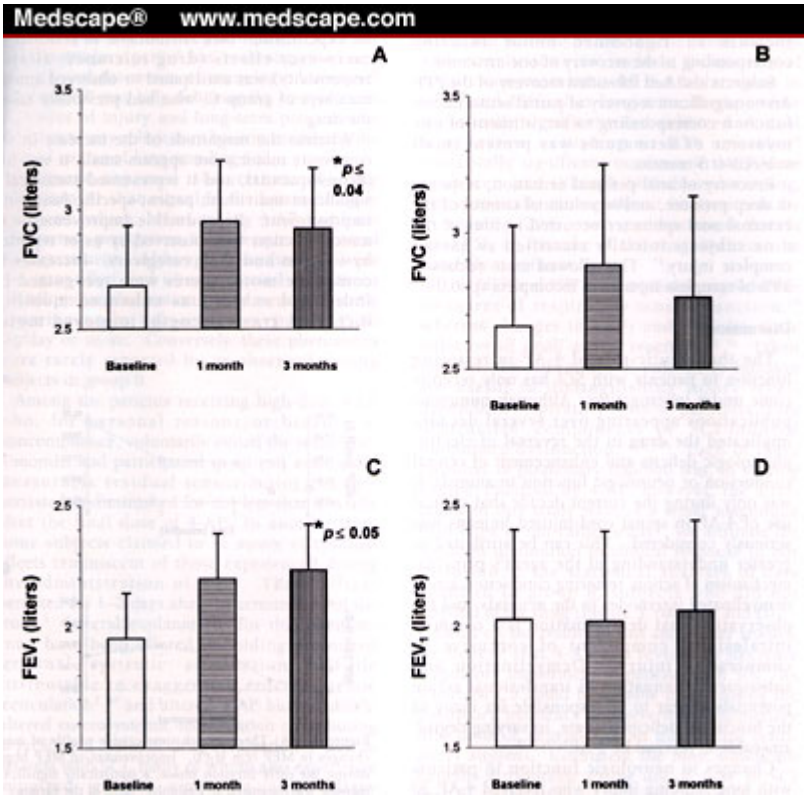

Figure 3. After 1 and 3 months of treatment with 4-AP, (A) FVC (L, mean ± SEM) and (C) FEV_1 (L, mean ± SEM) were significantly increased among all study subjects. Clinically meaningful improvements (American Thoracic Society criteria) were seen at 1 month, and persisted at 3 months when the high-dose subgroups, dosage-blinded and dosage-cognizant, were receiving 4-AP 30 mg/day. Neither mean FVC (B) nor FEV_1 (D) in the low-dose subgroup changed significantly or in a clinically meaningful way from baseline values. The 5-fold difference in amount of 4-AP administered appears to distinguish response from nonresponse.

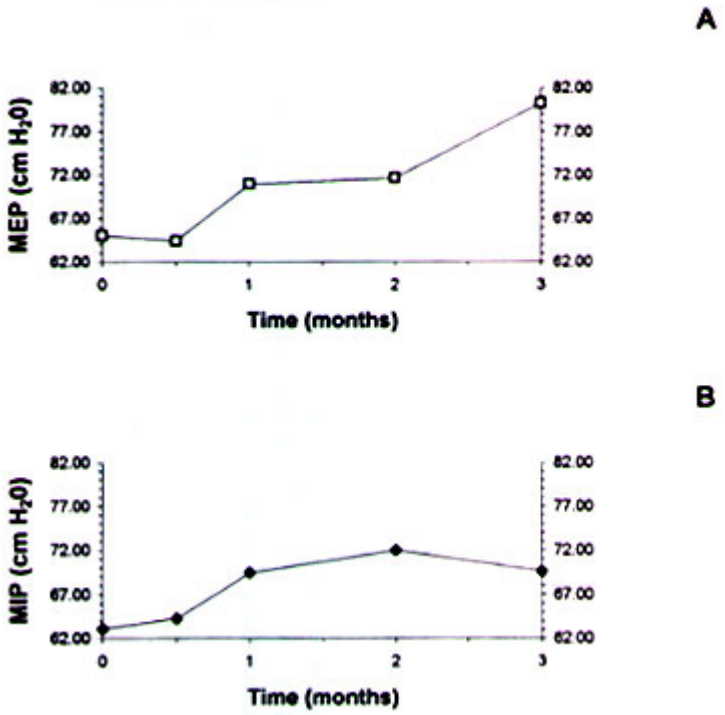

Figure 4. Three-month time-course profile of mean changes in MEP (cm H_2O). Improvement in MEP began during the early titration phase; a statistically significant increase was measured at 3 months. Most of the variance in MEP was attributable to groups A and C. (B) Changes in mean MIP (cm H_2O) in all subjects over 3 months. Improvements in MIP occurred in the early titration phase. Measurable increases, however, did not achieve statistical significance during 3 months of treatment and were never of the same order of magnitude as those seen in MEP.

Mean pretreatment FEV_1 (L/min), FVC (L), and MEP (cm H_2O) in all subjects increased from 2.0 ± 0.8 to 2.2 ± 1.0 ($p=0.06$), 2.7 ± 1.1 to 2.9 ± 1.2 ($p=0.04$), and 65.1 ± 44.4 to 70.9 ± 59.8 ($p<0.01$), respectively. These changes corresponded to increases of 15% in FEV_1, 9% in FVC, and 9% in MEP over baseline values. Nonsignificant differences ($p=0.33$) were observed in MIP. The magnitude of the mean values and percentage change in PFTs was diminished by the contribution of the low-dose subgroup in which no change was seen. Statistically significant or clinically meaningful changes in FEV_1, FVC, and MEP reflected improvements in pulmonary function and respiratory muscle strength among all subjects, including group B. Subjects in group B, however, who received 4-AP 6 mg/day, showed no improvements in FEV_1, FVC, MIP, or MEP by either statistical or ATS criteria.

Secondary Outcome Measures

The median modified Ashworth Score decreased by 26% from 2.6 ± 1.5 to 1.9 ± 1.7 in all subjects after 3 months of treatment with 4-AP. A statistically significant difference between medians was present with a p value less than 0.04 for the difference. Post hoc analyses were unable to exclude, at the 95% level of certainty, a drug-induced response in

group B as having contributed to the significance of the overall probability value at 3 months. Whereas overall mean pain score changed in parallel with Ashworth spasticity scores, indicating a decrease from pretreatment values at 3 months, the change in pain perception was statistically nonsignificant.

Previously insensate dermatomes and decentralized myotomes showed recovery and normal or near normal responsiveness to stimulation or volitional effort. Whereas recovery was observed bilaterally, it was significant only on the right side. Right-sided sensory ZPP progressed from T12 to L4. This change corresponded to a significant caudal progression of the sensory ZPP and was associated with a statistically significant caudal recruitment of partial sensory perception ($p=0.02$). It reflected a mean recovery of sensory perception in four contiguous segmental dermatomes, and was associated with a mean increase in right-sided motor function corresponding to the recovery of one myotome.

Subjects also had left-sided recovery of the ZPP. A nonsignificant recovery of partial sensorimotor function corresponding to recruitment of one myotome or dermatome was present in all subjects at 3 months.

Recovery of anal-perianal sensation, response to deep pressure, and/or volitional control of the external anal sphincter occurred in four of the nine subjects initially classified as having complete injury.[17] This allowed us to reclassify 44% of complete injuries to incomplete ($p=0.04$).

Discussion

The therapeutic role of 4-AP in restoring function to patients with SCI has only recently come under investigation. Although numerous publications appearing over several decades implicated the drug in the reversal of electro-physiologic deficits and enhancement of central conduction or neurologic function in animals, it was only during the current decade that clinical use of 4-AP in spinal cord-injured humans was seriously considered. This can be attributed to greater understanding of the agent's principal mechanism of action, restoring conduction across demyelinated internodes in the neuraxis, and the observation that demyelination is a common intralesional component of contusive or compressive injury.[5] Demyelination and subsequent attenuation of translesional action potentials appear to be responsible for many of the functional deficits that are, in varying degree, amenable to reversal by 4-AP.[2-4, 12, 15]

Changes in neurologic function in patients with long-standing injury who received 4-AP 30 mg/day support its role as an effective intervention in reversing functional deficits. In this study, statistically significant changes in sensorimotor function were perceptible to patients as useful enhancements of sensory perception and volitionally directed behaviors previously unattainable. Contrary to dogma that only acknowledges a 30% response rate to 4-AP in patients with incomplete injuries, we found, as in earlier studies, that when poorly understood or incompletely assessed pathophysiologic sequelae of SCI (impaired pulmonary function, gait disturbances, altered heart rate variability) are investigated, a

response to 4-AP may be seen in all subjects, regardless of completeness of injury.[2, 23, 24] Each subject had a response in one or more outcome measures, and no evidence of an experimental bias attributable to residual or carry-over effects (drug tolerance, altered responsivity) was anticipated or observed among members of group C, who had previously taken the drug.

Whereas the magnitude of the increase in the composite motor score appears small, it was not inconsequential, and it represented statistically significant individual, patient-specific functional improvement. Reproducible improvements in motor function were observed by us or reported by subjects and their caregivers. Increases in composite motor scores were recognized by individual subjects as enhanced mobility, increased grasp strength, improved motor coordination, refined truncal balance, and facilitated transfers. Enhanced bowel and bladder function translated into improved volitional control and reduced time required to complete bowel care.

Subjective awareness of the segmental reacquisition of cutaneous and/or deep sensation, often initially noxious or dysesthetic, correlated with caudal progression and recovery of the ZPP and an increase in the perception of pinprick in dermatomes that were insensate before administration of 4-AP. Recovery or persistence of the capability to recognize pinprick in the early postinjury period has been suggested as a predictor of the return of neurologic function.[25] Hence, 4-AP may help delineate the completeness or extent of injury and long-term prognosis in addition to any role it may have in modifying the natural course of long-standing SCI.

Subjects reported the return of deep sensation(s) that signaled the onset of body functions, which, before taking 4-AP, had been involuntary, precipitous, and a frequent source of embarrassment. Although these findings were not quantified and often reflected empiric or serendipitous observations, they were commonly experienced by subjects receiving 4-AP 30 mg/day or more. Conversely, these phenomena were rarely reported by or observed among subjects in group B.

Among the patients receiving high-dose 4-AP who, for personal reasons or because of noncompliance, voluntarily exited the study after 3 months and participated in an exit evaluation, measurable residual sensorimotor changes persisted undiminished for not less than 2 weeks after the final dose of 4-AP. In another trial, some subjects claimed to be aware of residual effects reminiscent of those experienced during the administration of 4-AP. These effects persisted for 1-2 days after the termination of the study.[3] Several explanations for this phenom-enon have been offered, including prolonged terminal systemic elimination half-life attributable to exaggerated enterosystemic recirculation[3, 12] and altered 4-AP bioavailability. Altered enterosystemic recirculation contributing to prolonged systemic drug elimination is seen in patients with SCI, many of whom also experience impaired gastric emptying and biliary dysfunction.[26-29] However, altered population-specific 4-AP pharmacokinetics or disposition cannot reasonably be invoked as an explanation for the persistence of effect observed after 2 weeks of abstinence. Other poorly understood or unidentified mechanisms should be sought. Central nervous system sequestration of active drug, altered synaptic mechanisms, and changes in the number,

molecular configuration, or sensitivity of axonal ion channels may mediate this phenomenon.

Administration of 10 mg of an immediate-release formulation of 4-AP was associated with sustained enhancements in PFTs and improved respiratory muscle strength that persisted for not less than 24 hours.[2] The results of the present study corroborate the findings of our single-dose study and allow us to extrapolate those findings and conclusions to include 3 months of continuous treatment with 4-AP. Increases in FEV_1 and FVC after long-term therapy were statistically significant and achieved clinical significance according to ATS criteria.[18] Statistically significant increases in MEP were again seen, and although MIP showed a strong, but statistically nonsignificant improvement by increasing 20% over pretreatment levels ($p=0.15$), an increase of this magnitude can be clinically significant.

Both MEP and MIP are quantitative, reproducible measures of respiratory muscle function,[19] whereas changes in FEV_1 and FVC are more reflective of small airway reactivity.[30, 31] Taken together, these measures of pulmonary function are useful in distinguishing injury level-dependent respiratory muscle paralysis from obstructive components of SCI-induced pulmonary dysfunction.[19, 30, 32] Each of these measures of pulmonary function was, in varying degree, changed by 4-AP; however, the alterations in this study were of a lesser magnitude than those in our earlier study.[2] We attribute the apparent diminution in clinical response to our inclusion in the statistical analyses of data acquired in group B, subjects who did not respond to the drug (Figure 3, panels B and D).

Based on the results of this and earlier studies, we believe that 4-AP can reverse or decrease respiratory impairment in patients with SCI. As a corollary, it could have value in decreasing the postinjury frequency and severity of pulmonary infections or dependence on mechanical ventilatory support. Ultimately, the most significant benefits attributable to the use of 4-AP in SCI may be those reflected in enhanced pulmonary function.

Secondary Outcome Measures

In our earlier study of 4-AP in patients with SCI, we reported significant, functionally useful improvements in individual gait parameters and bipedal locomotion.[23] We observed and corroborated, but did not experimentally measure, marked decreases in lower limb spasticity. Whereas spasticity is a sequela of SCI, it is not necessarily perceived as such by paretic, ambulatory patients who have adapted and learned to use spasm and increased muscle tone as an aid to locomotion.[33]

In the present study, we quantitatively measured spasticity and attributed statistical significance to the decrease in muscle hypertonus in our subjects. Whereas 4-AP may have a salutary effect on muscle spasm, it can deprive the patient of an important, albeit pathologic, adaptive mechanism. Many patients participating in this and the single-dose study immediately realized that the diminution in spasticity, initially uncomfortable and inconvenient, was only transiently so. In effect, they were able to restore more normal,

useful function by participating in more demanding, graded exercise, and felt that they were no longer as impeded by spasticity. Decentralized, hypertonic muscles could be brought back on line to help return body mechanics to normal and, most important, increase a patient's potential to advance to higher levels of useful function and rehabilitation.

Particularly noteworthy and intriguing was a change in neurologic classification from complete to incomplete injury. A statistically significant number of subjects achieved this transition during treatment with 4-AP. The mechanism(s) or physiologic changes mediating this phenomenon are unknown. It is, however, reasonable to postulate that the drug's action as an axonal ion channel blocker could be a major contributing factor to the recruitment of a requisite, threshold number of demyelinated, nonfunctional axons. Alternatively, or additively, 4-AP can improve neurologic function by enhancing synaptic transmission and increasing neuroneuronal and neuromuscular conduction.[34, 35] Drug-induced neurologic conversion of SCI status from complete to incomplete injury has not been reported previously and may have population-specific diagnostic and prognostic significance. The emotional benefits of neurologic reclassification or, for that matter, the recovery of any function, were incalculable to our patients.

Recovery of partial sensorimotor function in insensate, paralyzed segments contiguous with the pretreatment ZPP was unanticipated. To our knowledge, recruitment of new ZPPs and lowering of the neurologic level of injury in response to a drug has not been described in the literature. These results tend to substantiate and lend credibility to our finding of concomitant improvements in other measures of neurologic function in response to 4-AP.

Clinically significant adverse effects or measurable toxicity did not occur. Nervousness, giddiness or dizziness, and gastrointestinal upset manifesting as mild abdominal cramping or nausea were the most frequent side effects. Patients routinely reported mood elevation and an enhanced sense of well-being. Other clinical studies of 4-AP described similar positive effects on mood, and this potentially beneficial effect deserves further investigation. Except for the enhanced sense of well-being, which, once experienced, usually persisted unabated, all side effects were transient, self-limited, or disappeared with changes in dosage or the timing of drug ingestion to coincide with meals or snacks. Seizure or seizure-like activity was not observed nor was it reported by patients or caregivers at any time or at any dosage. Serially acquired EEG, ECG, biochemical and hematologic profiles, and urinalyses remained within normal range.

4-Aminopyridine is a potentially toxic drug with a narrow therapeutic index. In reviewing our clinical experience with 4-AP, we have administered an oral formulation in amounts of up to 40 mg/day to more than 60 patients. Significant toxicities or adverse reactions that warranted discontinuing a subject were never seen. We attribute this record of safety to careful patient selection and our recognition of the need to implement individualized dosing regimens based on population-specific pharmacokinetic behavior.[12, 15, 36, 37]

The present study shows that previously published findings of improvements in

pulmonary function are reproducible[2] and that changes in PFTs persist undiminished during the long-term administration of immediate-release 4-AP to patients with long-standing SCI. Our data also support conclusions that the agent is well tolerated. It is probably effective in restoring significant sensorimotor function that persists undiminished and is not associated with significant toxicity during 3 months of therapy.

The results of this study have brought us several steps closer to validating the clinical utility of 4-AP as a prototypical drug for SCI. The long sought-after and elusive goal of a safe, effective drug to restore or enhance useful sensorimotor function may be attainable, and traumatic SCI may no longer need be considered as "an ailment not to be treated."[1]

Tables

Table 1. Patient Demographics and Covariates

4-AP dosage	Age (yrs)	Height (cm)	Weight (kg)	Injury Duration (mo)	Neurologic Level of Injury Motor	Sensory	ASIA/IMSOP Classification
Group A	45	182.9	82.7	125	L3	L1	Incomplete
30 mg/day	61	180.3	103.6	192	C3	C3	Complete
dosage-	71	178.9	86.4	589	T9	T9	Complete
blinded	38	188.0	84.1	228	C5	T6	Incomplete
(n=6)	61	177.0	58.2	36	C8	C4	Incomplete
	35	182.9	79.6	194	C6	C4	Incomplete
Mean	51.8	179.7	82.4	227.3			
SD	14.5	6.5	14.6	189.9			

ASIA/IMSOP = American Spinal Injury Association/International Medical Society of Paraplegia

References

1. Breasted JH, ed. Case thirty-one. First description of quadriplegia. Case of dislocation of cervical vertebra. Circa 3000 B.C. In: The Edwin Smith surgical papyrus. Chicago: University of Chicago Press, 1930.
2. Segal JL, Brunnemann SR. 4-Aminopyridine improves pulmonary function in quadriplegic humans with long-standing spinal cord injury. Pharmacotherapy 1997;17(3):415-23.
3. 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;19:1-18.
4. Schwid SR, Petrie MD, McDermott MP, Tierney DS, Mason DH, Goodman AD. Quantitative assessment of sustained-release 4-aminopyridine for symptomatic treatment of multiple sclerosis. Neurology 1997;48:817-21.
5. Bunge RP, Puckett WR, Bercerra 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. In: Seil FJ, ed. Advances in neurology, vol 59. New York: Raven Press, 1993:75-89.
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. 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(2):553-62.
8. Bostock H, Sears TA, Sheratt RM. The effects of 4-aminopyridine and tetraethylammonium ions on normal and demyelinated mammalian nerve fibers. J Physiol 1991;313:301-15.
9. Stefoski D, Davis FA, Fitzsimmons WE, Luskin SS, Rush J, Parkhurst GW. 4-Aminopyridine in multiple sclerosis: prolonged administration. Neurology 1991;41:1344-8.
10. Targ EF, Kocsis JD. 4-Aminopyridine leads to restoration of conduction in demyelinated rat sciatic nerve. Brain Res 1985:328:358-61.
11. Blight AR, Toombs JP, Bauer MS, Widmer WR. The effects of 4-aminopyridine on neurologic deficits in chronic cases of traumatic spinal cord injury in dogs: a phase I clinical trial. J Neurotrauma 1991;8:103-9.
12. Potter PJ, Hayes KC, Hsieh JTC, 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.
13. Noordenbos W, Wall PD. Diverse sensory functions with an almost totally divided spinal cord. A case of spinal cord transection with preservation of part of one anterolateral quadrant. Pain 1976;2:185-95.
14. Young W. Recovery mechanisms in spinal cord injury: implications for regenerative therapy. In: Seil FJ, ed. Neural regeneration and transplantation. New York: AR Liss, 1988:157-69.
15. 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(10):837-49.
16. Joyce CRB. Placebos and other comparative treatments. Br J Clin Pharmacol 1982;13:313-18.
17. American Spinal Injury Association-International Medical Society of Paraplegia. International standards for neurological and functional classification of spinal cord injury, 4th ed. Chicago: American Spinal Injury Association, 1996.
18. American Thoracic Society. Lung function testing: selection of reference values and interpretative strategies. Am Rev Respir Dis 1991;144:1202-18.
19. Black LF, Hyatt RE. Maximal respiratory pressures: normal values and

relationship to age and sex. Am Rev Respir Dis 1969;99:696-702.
20. Bohannon RW, Smith MB. Interrater reliability of a modified Ashworth scale of muscle spasticity. Phys Ther 1987;67(2):206-7.
21. Ashworth B. Preliminary trial of carisoprodol in multiple sclerosis. Practitioner 1964;192:540-2.
22. Gibbons JD, ed. Nonparametric statistical inference, 2nd ed. New York: Marcel Dekker, 1985.
23. 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.
24. Segal JL, Brunnemann SR. The effects of 4-aminopyridine on heart rate and heart rate variability in humans with spinal cord injury. J Spinal Cord Med 1997;20(1):163.
25. Crozier KS, Graziani V, Ditunno JF Jr, Herbison GJ. Spinal cord injury: prognosis for ambulation based on sensory examination in patients who are initially motor complete. Arch Phys Med Rehabil 1991;72(2):119-21.
26. Williams W, Apstein M, Chassin S, et al. Gallbladder motility in spinal cord injury patients. J Nucl Med 1987;28:P596.
27. Segal JL, Brunnemann SR, Eltorai IM, Vulpe M. Decreased systemic clearance of lorazepam in humans with spinal cord injury. J Clin Pharmacol 1991;31:651-6.
28. Milne N, Segal JL, Rypins EB, Brunnemann SR, Lyons KP. Biliary kinetics in spinal cord injury (SCI). J Nucl Med 1987;28:688.
29. Segal JL, Milne N, Brunnemann SR. Gastric emptying is impaired in patients with spinal cord injury. Am J Gastroenterol 1995;90(3):466-70.
30. Bluechardt MH, Wiens M, Thomas SG, Plyley MJ. Repeated measurements of pulmonary function following spinal cord injury. Paraplegia 1992;30:768-44.
31. Roth EJ, Lu A, Primack S, Oken J, et al. Ventilatory function in cervical and high thoracic spinal cord injury. Relationship to level of injury and tone. Am J Phys Med Rehabil 1997;76(4):262-7.
32. Bergofsky EE. Mechanism for respiratory insufficiency after cervical cord injury: a source of alveolar hypoventilation. Ann Intern Med 1964;61:435-7.
33. Dietz V, Wirz M, Jensen L. Locomotion in patients with spinal cord injuries. Phys Ther 1997;77(5):508-16.
34. Jankowska E, Lundberg A, Rudomin P, Sykova E. Effects of 4-aminopyridine on synaptic transmission in the cat spinal cord. Brain Res 1982;240:117-29.
35. Molgo J, Lundh H, Thesleff S. Potency of 3,4-diaminopyridine and 4-aminopyridine on mammalian neuromuscular transmissions and the effect of pH changes. Eur J Pharmacol 1980;61:25-34.
36. Gumbleton M, Sneader W. Pharmacokinetic considerations in rational drug design. Clin Pharmacokinet 1994;26(3):161-8.
37. van Diemen HAM, Polman CH, Koetsier JC, et al. 4-Aminopyridine in patients with multiple sclerosis: dosage and serum levels related to efficacy and safety. Clin Neuropharmacol 1993;16:195-204.><#><PHARMACOTHERAPY Volume 19, Number 6, 1999><From the Departments of Medicine and Spinal Cord Injury Service, Department of Veterans Affairs Medical Center, Long Beach, California (all authors); the Department of Medicine, University of California, Irvine,

California (Drs. Segal, Hernandez, and Himber, and Ms. Brunnemann); and the Department of Neurorehabilitation, University of California, Los Angeles, California (Dr. Pathak).

Acknowledgements

We express our appreciation to Penny Shafer, Pharm.D., research pharmacist, and Steven D. Chretien, Pharm.D., Chief, Clinical Pharmacy, Pharmacy Service, Department of Veterans Affairs Medical Center, Long Beach, for their contributions. We acknowledge Toni Mandala, C.N.P., and Eloise Knoll, R.N., for their assistance. Our thanks to FMC Corporation for donating Avicel Ph-101 microcrystalline cellulose (NF).

Reprint Address

Address reprint requests to Jack L. Segal, M.D., (111GM), Department of Veterans Affairs Medical Center, 5901 East Seventh Street, Long Beach, CA